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Original Article

Paediatrics Section

Local Side Effects of Inhaled Budesonide in Asthmatic Children- A Cross-sectional Study

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ABSTRACT

Introduction: There is scarcity of Paediatric literature regarding local side effects of Inhaled Corticosteroids (ICSs) and available paediatric literature on the subject is old and has shown variable prevalence of these side effects varying from none to 60%.

Aim: To evaluate local side effects of inhaled Budesonide in asthmatic children of ≤12 years.

Materials and Methods: In this cross-sectional study, 250 asthmatic children attending Paediatric chest clinic of a tertiary care hospital and taking inhaled Budesonide for at least three months were evaluated for occurrence of local side effects during preceding one month. Local side effects (dysphonia, sore throat, cough during inhalation, thirsty feeling after inhalation, oral ulcers) experienced in preceding month were asked for and clinical evaluation for oral thrush, perioral dermatitis and tongue hypertrophy was done at the time of assessment. Information was collected regarding potential risk factors associated with occurrence of these side effects. Chi-square test was used to study the association between qualitative variables. Univariate and multivariate logistic regression were used to study the association between local side effects and potential factors associated with their occurrence.

Results: About 250 asthmatic children aged ≤12 years (64 children <6 years, 186 children ≥6 years) taking inhaled budesonide via pressurised Metered Dose Inhaler (pMDI) were evaluated. Almost half (48.8%) of the enrolled children experienced at least one local side effect, either daily or frequently, in the preceding month. Though majority experienced a single side effect, 21% experienced two or more side effects. Thirsty feeling after inhalation was the most common reported side effect experienced by 31.2% children followed by cough during inhalation, sore throat and dysphonia which were experienced by 25.2%, 17% and 8% children, respectively. Perioral dermatitis was found in only one patient while none of the patients had tongue hypertrophy or oral thrush. On univariate logistic regression, thirsty feeling after inhalation was associated with older age (≥6 years) and higher dose of Budesonide (>400 µg/day). Cough during inhalation was found to be associated with older age, higher dose of Budesonide, poor compliance to treatment and incorrect technique of taking pMDI and sore throat was associated with poor compliance and incorrect technique. However, on multivariate logistic regression, only cough during inhalation was found to be associated with higher dose of Budesonide and poor compliance to treatment.

Conclusion: Local side effects are common in asthmatic children using ICSs and should be routinely assessed during follow-up as a part of comprehensive asthma management plan.

Keywords: Asthma, Asthma medicines, Inhaled corticosteroids, Pressurised metered dose inhaler, Spacer

INTRODUCTION

The ICSs are the most effective controller medications available for treating asthma and are recommended as first line management option in children. However, systemic and local side effects of ICS do remain a concern especially at high doses. Systemic side effects of ICS are relatively well studied [1-5]. But paediatric literature on prevalence of local side effects is scarce, old and has shown variable prevalence ranging between none to 60% [6-9]. So the present study was planned primarily to assess the prevalence of local side effects of ICS among children less than 12 years of age attending Paediatric Chest Clinic of a tertiary care hospital and secondarily to determine the potential risk factors associated with their occurrence.

MATERIALS AND METHODS

This cross-sectional study was done in Paediatric Chest Clinic of a tertiary care hospital in Northern India from October 2017 to March 2019. Ethical clearance was obtained from Institutional Ethics Committee (IEC/VMMC/SJH/Thesis/October/2017-155).

Inclusion criteria: Children less than 12 years attending the paediatric chest clinic with a diagnosis of bronchial asthma (as per GINA 2016 guidelines [10]) and taking inhaled budesonide for at least three months were included in the study after taking informed consent from parents.

Exclusion criteria: Children with immunodeficiency (congenital or acquired) and chronic diseases (chronic lung disease, tuberculosis, diabetes mellitus) were excluded. Also children who were taking or had received oral/intranasal steroids or antibiotics in the preceding month were excluded.

Assuming a prevalence of 20% of local side effects of inhaled budesonide and precision of 5%, using the formula z^2pq/d^2, sample size of 250 was calculated to be sufficient to assess the prevalence of local side effects [6]. A pre-designed proforma was used to record patient characteristics. The local side effects (dysphonia, sore throat, cough during inhalation, thirsty feeling after inhalation, oral ulcers) experienced by the patient or perceived by the parents during preceding one month were asked for and the frequency of occurrence was classified as occurring never/occasionally (once in a while), frequently (most days of the week but not daily) and daily as used previously in few studies [6,11]. This history was supplemented with a clinical examination to look for oral thrush, perioral dermatitis and tongue hypertrophy, at the time of patient contact. Also, the study recorded information about dose and duration of budesonide use, technique of usage, compliance with treatment, use of Long Acting β2 -Agonists (LABA) and mouth rinsing after ICS use to assess the potential factors associated with occurrence of local side effects of ICS. Technique of using inhaled budesonide was assessed by using a five point checklist that has been used in a previous Paediatric study in India and is rountinly used in the clinic [12].

STATISTICAL ANALYSIS

Data was entered in Microsoft Excel and analysis was done using Statistical Package for the Social Sciences (SPSS) Software version 21.0. Chi-square test was used to study the association between qualitative variables. Univariate and multivariate logistic regression were used to study the association between local side effects and potential factors associated with their occurrence. Odds ratio with 95% confidence interval was computed for the same. The p-value of <0.05 was considered statistically significant.

RESULTS

A total of 250 asthmatic children aged ≤12 years (range-3 to 12 years) were evaluated. [Table/Fig-1] depicts demographic profile of the enrolled children. Thus, almost three-fourths of enrolled children were ≥6 years of age. All the patients were using inhaled budesonide through pMDI with or without valved holding chamber. Out of 75 patients on higher dose of Budesonide (≥400 µg), 54 (72%) were using it for longer duration (≥6 months) and this association was statistically significant (28% vs. 72%, p<0.0001). About 115 patients were using inhalers with correct technique. Regarding compliance, as many as 89 had poor compliance with ICS treatment. 53.6% (n=134) patients were not practicing mouth rinsing after use of inhaled budesonide.

Characteristic	N (%)
Age	
<6 years	64 (25.6%)
≥6 years	186 (74.4%)
Sex	
Male	143 (57.2%)
Female	107 (42.8%)
Device used for taking Budesonide	
pMDI with VHC	244 (97.6%)
pMDI with VHC with mask	2 (0.8%)
pMDI alone	4 (1.6%)
Budesonide dose	
≤400 µg/day	175 (70%)
>400 µg/day	75 (30%)
Duration of Budesonide use	
3-6 months	153 (61.2%)
6-12 months	65 (26%)
>12 months	32 (12%)
Use of LABA	20 (8%)

[Table/Fig-1]: Demographic profile of study population.
pMDI- Pressurised metered dose inhaler, VHC- Valved holding chamber, LABA- Long acting β2 agonist

Almost half (48.8%, n=122) of the enrolled children experienced at least one local side effect of ICS, either daily or frequently, in the preceding month. As many younger children (<6 years of age) reported side effects as older children (26/64, 40.6% vs 96/186, 51.6% in <6 years and 6-12 years, respectively, p-value 0.129 by chi-square test) [Table/Fig-2].

Age	Local side effects frequency	
	Never/Occasionally	Frequently/Daily
<6 years	38 (59.4%)	26 (40.6%)
≥6 years	90 (48.4%)	96 (51.6%)

[Table/Fig-2]: Frequency of local side effects observed in study population.

Thirsty feeling after inhalation was the most common reported side effect experienced by 31.2% (n=78) children followed by cough during inhalation, sore throat and dysphonia which were experienced by 25.2% (n=63), 17% (n=43) and 8% (n=20) children, respectively [Table/Fig-3]. Perioral dermatitis was found in only one patient while none of the patients had tongue hypertrophy or oral thrush. Most of the patients (n=68, 27.2%) experienced a single side effect. However, as many as 54 children (21%), experienced two or more side effect in the preceding month.

Side effect	Daily	Frequently	Never/Occasionally
Dysphonia	8 (3.2%)	12 (4.8%)	230 (92%)
Sore throat	7 (2.8%)	36 (14.4%)	207 (82.8%)
Cough during inhalation	31 (12.4%)	32 (12.8%)	187 (74.8%)
Thirsty feeling after inhalation	50 (20%)	28 (11.2%)	172 (68.8%)

[Table/Fig-3]: Profile of local side effect observed in study population.

All the side effects were reported more frequently by older children (>6 years) than younger ones. However, only cough during inhalation and thirsty feeling after inhalation were found to have statistically significant association with age. As expected, the association was statistically significant for cough during inhalation and thirsty feeling after inhalation {OR 3.798 (95% CI 2.080-6.934), p-value <0.0001 and OR 2.087 (95%CI 1.183-3.683), p-value 0.011, respectively}. None of the side effects were found to be associated with longer duration of budesonide use or use of LABA. Four children were using MDIs without spacer and all had cough during inhalation daily. Children with poor compliance to treatment generally reported side effects more frequently and association was statistically significant for sore throat {OR 4.468 (95% CI 2.230-8.949), p-value <0.0001} and cough during inhalation {OR 2.354 (95% CI 1.313-4.221), p-value 0.004}. Also, children taking pMDI incorrectly had more frequent occurrence of all side effects and this association was statistically significant for sore throat [OR 2.558 (95%CI 1.245-5.256), p value 0.011] and cough during inhalation [OR 2.443 (95% CI 1.328-4.495), p value 0.004] [Table/Fig-4,5].

On multivariate logistic regression, only cough during inhalation was found to be associated with higher dose of budesonide and poor compliance to treatment [Table/Fig-6].

DISCUSSION

Local side effects of ICSs include sore throat, dysphonia/hoarseness, cough during inhalation, thirsty feeling after inhalation, oral candidiasis, tongue hypertrophy and perioral dermatitis. Though considered minor and insignificant, local side effects can impair quality of life, affect compliance and interfere with assessment of asthma control [13,14]. The exact mechanisms leading to local side effects of ICSs are not known but various hypothesis have been postulated including non-specific irritant effect of ICS, pro-inflammatory effect of propellant and lubricant component of MDI, vocal cord dyskinesia, increased salivary glucose, decreased oral immunity and intrinsic inflammation of the upper airway in asthmatic patients [13,14]. Available literature on magnitude of these side effects is scarce especially in paediatric age group and has shown highly variable prevalence varying between 5-60%, probably related to steroid formulation, dose, delivery device and study methodology (questionnaire vs clinical examination) [6-9,13,14].

Present study showed high prevalence of local side effects of inhaled budesonide with almost half of the study children experiencing them. Comprehensive assessment of all local side effects of ICS in paediatric age group has been reported only in one study [6]. This study by Dubus JC et al., which showed prevalence of local side effects to be as high as 61.5% (63.3% in <6 years and 59.5% in >6 years) in children using either beclomethasone dipropionate or budesonide via variety of inhalation devices (pMDI with or without spacer, autohaler, (Dry Powder Inhaler) DPI or nebuliser) with beclomethasone dipropionate causing more side effects compared to budesonide. Present study, done on a more homogenous population (budesonide only, delivered via pMDI, mostly with spacer), showed similar high prevalence of local side effects. Rest of the paediatric studies have focused on individual side effects [7-9].

Characteristics	Cough during Inhalation				Thirsty feeling after inhalation			
	Yes N (%)	No N (%)	p-value	OR (95%CI)	Yes N (%)	No N (%)	p-value	OR (95%CI)
Age								
<6 years	10 (15.6)	54 (84.4)			12 (18.8)	52 (81.2)		
6-12 years	53 (28.5)	133 (71.5)	0.044	2.152 (1.020-4.538)	66 (35.5)	120 (64.5)	0.014	2.383 (1.188-4.780)
Budesonide dose								
≤400 µg/day	30 (17.1)	145 (82.9)			46 (26.3)	129 (73.7)		
>400 µg/day	33 (44)	42 (56)	<0.0001	3.798 (2.080-6.934)	32 (42.7)	43 (57.3)	0.011	2.087 (1.183-3.683)
Duration of budesonide use								
<6 months	41 (26.8)	112 (73.2)			48 (31.4)	105 (68.6)		
6-12 months	16 (24.6)	49 (75.4)	0.737	0.892 (0.457-1.740)	19 (29.2)	46 (70.7)	0.754	0.904 (0.479-1.704)
>12 months	6 (18.8)	26 (81.2)	0.345	0.630 (0.242-1.642)	11 (34.4)	21 (65.6)	0.740	1.146 (0.512-2.564)
LABA use								
No	57 (24.8)	173 (75.2)			72 (31.3)	158 (68.7)		
Yes	6 (30)	14 (70)	0.607	1.301 (0.478-3.543)	6 (30)	14 (70)	0.904	0.940 (0.347-2.547)
Compliance								
Good	31 (19.3)	130 (80.7)			48 (29.8)	113 (70.2)		
Poor	32 (36)	57 (64)	0.004	2.354 (1.313-4.221)	30 (33.7)	59 (66.3)	0.525	1.197 (0.688-2.084)
Technique								
Correct	19 (16.5)	96 (83.5)			37 (32.2)	78 (67.8)		
Incorrect	44 (32.6)	91 (67.4)	0.004	2.443 (1.328-4.495)	41 (30.4)	94 (69.6)	0.759	0.919 (0.538-1.572)

[Table/Fig-4]: Univariate logistic regression showing association of cough during inhalation and thirsty feeling after inhalation with potential associated factors.
OR- Odds ratio, 95% CI- 95% confidence interval, LABA- Long acting β2 agonist

Characteristics	Dysphonia				Sore throat			
	Yes N (%)	No N (%)	p-value	OR (95% CI)	Yes N (%)	No N (%)	p-value	OR (95% CI)
Age								
<6 years	1 (3.1)	63 (96.9)			11 (17.2)	53 (82.8)		
6-12 years	19 (10.2)	167 (89.8)	0.057	7.168 (0.940-54.66)	32 (17.2)	154 (82.8)	0.998	1.001 (0.472-2.125)
Budesonide dose								
≤400 µg/day	11 (6.3)	164 (93.7)			25 (14.3)	150 (85.7)		
>400 µg/day	9 (12)	66 (88)	0.133	2.033 (0.805-5.133)	18 (24)	57 (76)	0.065	1.895 (0.962-3.734)
Duration of budesonide use								
<6 months	11 (7.2)	142 (92.8)			23 (15)	130 (85)		
6-12 months	5 (7.7)	60 (92.3)	0.896	1.076 (0.358-3.230)	18 (27.7)	47 (72.3)	0.061	2.165 (0.974-4.364)
>12 months	4 (12.5)	28 (87.5)	0.323	1.844 (0.548-6.209)	2 (6.3)	30 (93.7)	0.202	0.377 (0.084-1.686)
LABA use								
No	17 (7.4)	213 (92.6)			38 (16.5)	192 (83.5)		
Yes	3 (15)	17 (85)	0.240	2.211 (0.589-8.302)	5 (25)	15 (75)	0.340	1.684 (0.578-4.911)
Compliance								
Good	9 (5.6)	152 (94.4)			15 (9.3)	146 (90.7)		
Poor	11 (12.4)	78 (87.6)	0.065	2.382 (0.947-5.990)	28 (31.5)	61 (68.5)	<0.0001	4.468 (2.230-8.949)
Technique								
Correct	6 (5.2)	109 (94.8)			12 (10.4)	103 (89.6)		
Incorrect	14 (10.4)	121 (89.6)	0.142	2.102 (0.780-5.661)	31 (23)	104 (77)	0.011	2.558 (1.245-5.256)

[Table/Fig-5]: Univariate logistic regression showing association of dysphonia and sore throat with potential associated factors.
OR- Odds ratio, 95%CI- 95% confidence interval, LABA- Long acting β2 agonis

Thirsty feeling after inhalation of ICSs, experienced by almost one third of enrolled children emerged as the most common reported local side effect in present study. Also, it occurred more commonly in older children (>6 years) and those on higher dose of budesonide (>400 mcg/day). This side effect has not been well researched upon and has been hypothesised to be due to throat irritation or early symptom of oral candidiasis [6,13,14]. Study by Dubus JC et al., reported this side effect in 21.9% and 41.5% of study subject, respectively [6]. Higher occurrence in older age group seen in present study could be due to better perception and reporting compared to younger age group. Higher oropharyngeal deposition with higher dose of budesonide may explain the association with higher dose.

Cough during inhalation of budecort was second most common reported side effect and was associated with older age, higher dose of budesonide, poor compliance and incorrect technique of inhalation therapy. Postulated mechanisms for this side effect include toxic role of inhaled recipients (oleic acid) and non-specific irritant effect of ICS [6,13,14]. Study by Dubus JC et al., reported this side effect in 40% children using ICS and found it more commonly in younger age group and those using ICS with spacer device [6]. Another follow-up study done by same author to investigate influence of different factors on occurrence of post inhalation cough in children taking ICS with spacer device found this side effect in almost 50% children and found it to be associated with longer duration of ICS use and use of LABA [7].

Characteristic	Cough during Inhalation		Thirsty feeling after inhalation		Sore throat	
	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)
Age						
<6 years						
6-12 years	0.256	1.558 (0.732-3.532)	1.000	1.923 (0.022-8.366)	-	-
Budesonide dose						
≤400 µg/day						
>400 µg/day	0.0001	3.711 (1.940-7.217)	1.000	2.235 (0.057-5.096)	-	-
Compliance						
Good						
Poor	0.044	1.934 (1.018-3.687)	-	-	0.930	1.158 (0.006-6.806)
Technique						
Good						
Poor	0.162	1.635 (0.821-3.311)	-	-	0.338	1.295 (0.073-1.117)

[Table/Fig-6]: Multivariate logistic regression showing association of different local side effects with risk factors found significant on univariate logistic regression.
OR: Odds ratio; 95% CI: 95% confidence interval

Sore throat and dysphonia, most common documented side effects of ICS in literature, were reported by 17% and 8% children respectively in present study. Pathophysiology of ICS associated dysphonia may involve steroid induced myopathy affecting vocal cord muscles (manifesting as bilateral adductor fold deformity with bowing of vocal cords on phonation), mucosal irritation (manifesting as mucosal edema, erythema, interarytenoid mucosal thickening, granulations) and less commonly laryngeal candidiasis [6,13-17]. There was no association of dysphonia with any of the risk factors studied but sore throat was more common in those with poor compliance with treatment and incorrect technique of taking MDI. Dubus JC et al., reported hoarseness and dysphonia in 14% and 11% children in their study and found dysphonia to be associated with higher dose of ICS, use of space device/nebuliser and hoarseness with longer duration of ICS use and older age [6]. In contrast Agertoft L et al., did not find any difference in occurrence of hoarseness/other voice symptoms in asthmatic children using/not using ICS with these symptoms present in 20% and 21% of users and nonusers, respectively [9].

Only one child had perioral dermatitis and none had oral thrush or tongue hypertrophy in present study. Perioral dermatitis is hypothesised to be due to direct effect of inhaled steroids on facial skin. It is an uncommon side effects of ICS reported by Dubus JC et al., in about 3% of study children and in some case reports [6,18,19]. Tongue hypertrophy, postulated to be due to direct effect of ICS causing tongue muscle hypertrophy or local fat accumulation, is even rarer and has been reported only in isolated case reports and in one out of 639 children studied by Dubus JC et al., [6,13,14,20]. Increased incidence of candida colonisation/thrush in ICS users may be due to decreased local immunity or increased salivary glucose. Though paediatric studies have shown increased rates of colonisation with *Candida* after treatment with ICS, clinical oral thrush has been reported variably ranging from none to 10% [6,8,21].

Present study is one of the few Paediatric studies done to evaluate local side effects of ICSs. Strengths of present study are inclusion of large number of children and a more homogenous population of children (using only Budesonide via pMDI only and mostly with valved holding chambers) as compared to previous studies [6-9]. As available Paediatric literature on local side effects of ICSs has shown variable association of these side effects with potential risk factors, more studies are required to assess the factors associated with occurrence of these side effects, so as to institute appropriate preventive measures.

Limitation(s)

Present study was done at a tertiary care hospital and thus might have included more children with higher disease severity and thus generalisability of results to the whole spectrum of asthma severity in community setting might be affected.

CONCLUSION(S)

Local oropharyngeal side effects of ICS are common in paediatric population. Evaluation of these local side effects should be part of comprehensive management of asthmatic children on ICS therapy.

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