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Title: Effect of vitamin D correction on control of asthma in vitamin D deficient pediatric asthma patients
Running Title: Effect of Vitamin D on asthma control

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ABSTRACT
BACKGROUND: The effect of vitamin D supplementation on control of asthma has been studied in few observational studies. The present study aims to determine the effect of Vitamin D correction in Vitamin D deficient pediatric asthmatic patients in terms of reduction of exacerbation, improvement in pulmonary function test (PFT) and reduction in dosage of inhaled corticosteroids (ICS).
METHODS: A prospective interventional study was conducted on 20 vitamin D deficient asthmatic children aged 5-12 years receiving standard therapy for at least 12 months and parameters of asthma control, need for rescuer therapy were compared pre- and post-vitamin D correction. A detailed questionnaire including exacerbations, emergency visits, use of rescuer therapy in the previous 12 months was documented. Baseline PFT, CBC, LFT and KFT were obtained. Study participants received 60,000 IU of cholecalciferol weekly x 6 weeks followed by 600 IU/day and calcium supplementation 600-800 mg/day for three months.
RESULTS: Out of 20 children 10 had severe, 8 had moderate while 2 had mild asthma. After treatment with corrective dose of Vitamin D for 3 months, there was statistically significant improvement in PFT and reduction in dose of ICS (p value <0.001). There was decrease in number of average monthly emergency hospital visits, admissions and use of rescuer therapy after correction (p value < 0.001).
CONCLUSION: The replenishment of vitamin D stores in vitamin D deficient asthmatic children is associated with improvement in asthma control in terms of % predicted FEV1, reduction in daily ICS and significant reduction in number of exacerbations.
Key words: asthma, exacerbation, vitamin D

I. INTRODUCTION

Asthma is one of the most common and debilitating chronic respiratory disorder of pediatric age group. In the last 2-3 decades there has been increase in the incidence of clinically diagnosed asthma in children and adolescents from 4.16 % to 17.14% [1] Pediatric asthma causes hindrance in the overall growth potential of the child affecting their studies, recreation and self- imposed isolation from the peer groups. In last decade there has been mounting evidence on role of vitamin D as immunomodulator in childhood asthma [2-4]. Vitamin D is an immunomodulator and Vitamin D receptors (VDRs) present in cells of immune system regulate transcription of genes to promote synthesis of anti – inflammatory cytokines such as interleukin-10 (IL-10) and suppress pro-inflammatory cytokines

Studies on association between low vitamin D levels and increase severity of asthma symptoms come from observational cohorts [5-7]. The effect of vitamin D supplementation on various parameters of severity in childhood asthma has been studied in few interventional studies. So, we conducted a study to know the effect of vitamin D

correction on exacerbation of asthma and use of rescuer therapy in children with bronchial asthma.

II. MATERIALS AND METHODS

Study Design and Participants

This was a prospective interventional study conducted at tertiary care teaching hospital in New Delhi, India from September 2017 to February 2019. The study was approved by Institutional ethics board. Written informed consent was obtained from parent or legal guardian of each participant before enrollment. Children with bronchial asthma aged 5-12 years under standard therapy for twelve or more months with regular follow-up in pediatric chest clinic and good treatment compliance were screened for vitamin D status. 25 (OH) D concentration of >20 ng/mL (50 nmol/L) were considered as sufficient, between 12-20 ng/mL (30-50 nmol/L) as insufficient and <12 ng/mL (<30 nmol/L) as deficient according to IAP guidelines [8]. Among the screening population, those with serum 25(OH) D level < 12 ng/ml i.e. Vitamin D deficient were enrolled for the study. Children with poor compliance or faulty technique of use of metered dose inhaler (MDI), on vitamin D supplementation, with chronic renal disease or disorder of calcium or bone metabolism, history of phenytoin or phenobarbitone intake, who had fracture in recent past were excluded from the study.

Detailed questionnaire regarding history of exacerbation in the previous twelve months were documented and verified from their treatment files. Acute exacerbation was defined as an asthma related hospitalization, visit to the emergency department or use of rescuer therapy. At the time of enrollment patient's baseline pulmonary function test (PFT) and dose of inhaled corticosteroids (ICS) were documented. Patient's baseline complete blood count, liver function tests, kidney function tests were obtained. Serum vitamin D levels along with serum calcium, phosphate and alkaline phosphatase were measured. Study participants were treated with oral vitamin D, (60,000 IU weekly x 6 weeks followed by 600 IU /day) and oral calcium supplement (600-800 mg / day) for three months as per Indian Academy of Pediatrics guidelines [8]. Oral vitamin D was administered as dry powder in sachets of 60,000 IU each. Children were kept under monthly follow up and compliance to therapy assured by return of empty sachets each month. Correction in Vitamin D levels was assessed at the end of three months by measuring serum 25(OH) D level. Any new exacerbation in terms of emergency hospital visits, hospital admissions or use of rescuer therapy was recorded. At the end of the study, a repeat detailed questionnaire regarding exacerbations during study period was filled. It was verified from the records of chest clinic as well. Participant's pulmonary function status, dose of ICS was compared with baseline parameters obtained at the start of study. Figure 1 shows the outline of the study.

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 21.0. Continuous variables were presented as the mean ±standard deviation (SD) or median (minimum–maximum) while categorical variables were presented as the frequency and percentage. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Using statistical tests, the statistical significance of each parameter was assessed independently. Initial vitamin D value was compared using ANOVA Test (as the data sets were normally distributed) between the severity of asthma and paired t test/ Wilcoxon signed rank test was used for comparison of initial and final values. Qualitative variables were correlated using Chi-Square test. A p value of <0.05 was considered statistically significant.

III. RESULTS

Fifty-three asthmatic children of 5-12 years age who were on standard therapy for twelve or more months were screened for vitamin D status. Mean age of patients was 10.25 ±0.97 years. Out of 53 children, 34 [64%] were male. 8 were of mild asthma, 29 were of moderate asthma and 16 had severe asthma. The mean vitamin D level of 53 asthmatic children was 18.62 ± 8.45 ng/ml. Among these 37.74 % had vitamin D deficiency, 28.30 % had insufficiency and 33.96 % had sufficient levels of Vitamin D. Table 1 shows the baseline characteristics and biochemical profile of study participants.

Out of 16 patients with severe asthma screened for vitamin D deficiency, 10 patients (62.50%) were Vitamin D deficient while the remaining 6 (37.5%) were vitamin D insufficient. None of the patients with severe asthma had normal serum vitamin D levels. In the case of moderate asthma out of 29 patients screened, 8 patients (27.59%) were vitamin D deficient. In mild asthma group 2 out of 8 patients (25%) were vitamin D deficient while remaining had vitamin D in normal range. Mean initial vitamin D level in mild asthmatic children was 27.225 ng/ml, in moderate asthmatic children was 19.696 ng/ml and in severe asthmatic was 12.368 ng/ml. There was statistically significant difference in mean levels of

vitamin D among mild, moderate and severe asthmatic children (p value 0.002).

20 asthmatic children were found to have vitamin D levels < 12ng/ml (10 had severe asthma, 8 moderate and 2 had mild asthma). They underwent further evaluation and were given vitamin D supplementation. In all 20 patients, vitamin D level was corrected to normal range after 3 months and maintenance vitamin D and calcium were advised through diet. After treatment with corrective dose of vitamin D for 3 months there was statistically significant improvement in the vitamin D level from pre-treatment values (p<0.001) [figure 2]. Serum alkaline phosphatase levels measured at baseline and at 3 months decreased significantly from 237.45 ± 44.36 U/L to 153.25 ± 27.07 U/L (p value< 0.001)

The mean duration of follow up for study participants was 9.3 months. The mean forced expiratory volume in the first second (FEV1) was 0.95± 0.13 L, 1.16 ±0.11 L and 1.17 ±0.11L at baseline, 3 months and at end of study (p value <0.001) [Figure 3]. The initial average daily dose of inhaled corticosteroids decreased from 415 ± 138.7 µgm to 245 ±99.87 µgm (p value <0.001) after correction of vitamin D deficiency [Figure 4]. The average number of emergency visits observed at baseline among study participants was 0.24 ± 0.07 visit per month which decreased significantly to 0.06 ±0.06 visit per month (p value < 0.001) after correction with vitamin D at 3 months. Also, there was significant decrease in number of hospitalizations for exacerbation from pre-treatment to post treatment i.e.0.1 ±0.07 admission/month to 0.04 ±0.06 admission /month respectively (p value 0.002). The requirement of rescuer therapy decreased from average 4.3 ±1.53 times per month to 1.7 ±0.86 times per month after the correction of Vitamin D levels (p value <0.001) [figure 5]. Table 2. shows the comparison of biochemical profile, severity of asthma and parameters of exacerbation pre- and post-vitamin D treatment.

IV. DISCUSSION

The present study showed improvement in pulmonary function tests and decrease in steroid dose after replenishment of vitamin D stores in vitamin D deficient asthmatic children. Male to female ratio of study participants was 1.8 which is similar to previous studies on Indian children [9,10]

Of 53 asthmatic children screened, two-third had insufficiency or deficiency of vitamin D. Suchiang et al in their study found that 81.3% asthmatic children had severe Vitamin D deficiency while 16% had Vitamin D insufficiency[9]. Krishnan E et al in their study found 83.3 % asthmatic children as Vitamin D deficient in their study [10]. The cutoff to define Vitamin D deficiency is different among different studies. We used a lower cutoff as <12 ng/ml in accordance with IAP guidelines hence had lower proportion as vitamin D deficient as compared to other studies. The mean levels of vitamin D were significantly lower in severe asthmatics as compared to those with mild and moderate asthma. 62.5% of children with severe asthma, 27% of moderate asthma and 25% of children with mild asthma were vitamin D deficient. Suchiang et al [9] in their study also demonstrated negative correlation between serum vitamin D levels and severity of asthma. It has been shown in studies that lower vitamin D levels in asthmatic children were associated with worsening of airflow limitation and hence associated worsening of disease [7,10,11].

We found that correction of vitamin D led to improvement of PFT in asthmatic patients. There was statistically significant improvement in FEV1 at 3 months and end of study as compared to baseline. Studies in past on effect of vitamin D supplementation on pulmonary function status have revealed similar findings. Suchiang et al in their study categorized asthmatic children according to% predicted FEV1 i.e., <60%, 60-79 % and > 80%, the mean value of Vitamin D was found as11.50 ng/ml, 15.07 ng/ml and 19.79 ng/ml respectively. Vitamin D levels were significantly lower in children with severe airflow limitation [9]. Daniel A Searing et al showed positive correlation of predicted FEV1% and FEV1/forced vital capacity (FVC) ratio and Vitamin D levels [11]. Hou C et al observed that FEV1 in children with bronchial asthma was higher after treatment than before treatment [12]. These finding could be explained by the fact that Vitamin D receptors (VDR) are present in human bronchial smooth muscle cells [13] and expression of many genes involved in asthma are regulated by these. Improvement in Vitamin D levels lead to improved regulation by VDR and downregulation of pro-inflammatory cascade.

Daniel A searing et al studied variables associated with vitamin D deficiency in asthmatic children and found lower vitamin D levels associated with use of corticosteroids and worsening airflow limitation. They also studied in vitro effect of vitamin D on corticosteroid-mediated anti-inflammatory responses by testing whether vitamin D enhances glucocorticoid induction of mitogen-activated protein kinase (MAPK) phosphatase 1 (MKP-1) and IL-10 in

peripheral blood mononuclear cells using real-time PCR and T cell proliferation assay. Significant enhancement in DEX-induced mitogen-activated protein kinase (MAPK) phosphatase 1 (MKP-1) and IL-10 mRNA was observed following vitamin D pretreatment in peripheral blood mononuclear cell (PBMC) suggesting potentiation of immunosuppressive effect of Dexamethasone in-vitro. Jolliffe D A et al [4] performed a systemic review and meta-analysis on Vitamin D supplementation to prevent asthma exacerbations. The study showed that Vitamin D supplementation reduced the requirement of systemic corticosteroids among all the participants. Yue Huang et al suggested the molecular mechanism of this improvement through animal study. It was demonstrated that administration of Vitamin D improved the airway remodeling in asthma by down-regulating the activity of Wnt / B-catenin signaling pathway. There was reduced thickness of the airway smooth muscle, decrease collagen deposition and the alpha-smooth muscle actin (α-SMA) mass and hence decreased airway inflammation [3]. In our study we also found significant reduction in the dose of inhaled corticosteroids after correction of Vitamin D levels in all 20 asthmatic children. There was significant reduction in mean daily inhaled corticosteroid dose pretreatment from 415±138.7 microgram/day to 245 ±99.87 microgram/day after the correction of Vitamin D levels.

Krishnan E et al in their study found that there was marked reduction in emergency room visits, reliever medication usage at 3rd and 6th month after supplementation of Vitamin D in asthmatic children [10]. Majak et al [2] randomized 48 newly diagnosed asthmatic children to receive inhaled budesonide and vitamin D or inhaled budesonide alone. The authors observed that the number of children who experienced asthma exacerbation was significantly lower in the steroid+ D3 group than in the steroid group. In our study we observed that there was 75% reduction in number of emergency hospital visits after correction of vitamin D levels in study participants. Also, there was two third reduction in asthma related hospitalization and the need for rescuer therapy after treatment.

Though various observational studies in past have related vitamin D status as a variable for asthma exacerbation or with PFT's indices of severe asthma, most of these studies were cross sectional. Moreover, single measurements of 25(OH)D were performed and were correlated with parameters of asthma control. The current study is notable by the fact that only vitamin D deficient asthmatic children were recruited, the levels of 25(OH) D were documented after correction and pre- and post-treatment comparison of control of asthma was done. The limitation of the study are small sample size and a non-randomized study design.

V. CONCLUSION

The role of vitamin D in the development and management of asthma remains an active area of research. Our study shows that replenishment of vitamin D stores in vitamin D deficient asthmatic children is associated with improvement in asthma control in terms of % predicted FEV1, reduction in daily inhaled corticosteroid use and significant reduction in number of exacerbations. Further studies including larger participants are needed. Also, level of 25(OH)D level at which beneficial effects in either disease prevention or disease management can be definitively seen remains unclear, and more studies are needed.

What is known?

1. Vitamin D deficiency is common in childhood asthmatics.
2. Vitamin D deficiency is associated with higher odds of severe asthma exacerbation.

What this study adds?

- Replenishment of vitamin D stores confers protection against exacerbation and reduction in daily dose of inhaled steroids over 12-month period.

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Contributions : AK and RG were consultant in-charge. SP and AK conceived the idea. SP collected the data. SR did the biochemical analysis. SP, AK, NC and KK reviewed the literature, and drafted the manuscript. AK and RG critically reviewed the manuscript and gave final approval of the version to be published.

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TABLEs:

Table 1. Baseline characteristics and biochemical profile of study participants (n=53)

Characteristic	Value
Age in years; mean ± SD	10.25 ± 0.97
Male: female, n	34:19
BMI, kg/m^2; mean ± SD	16.3 ± 2.7 kg/m^2
25OHD level (ng/ml); mean ± SD	18.62 ± 8.45
Vitamin D status Sufficient - (25(OH) D >20 ng/mL), n (%) Insufficient - (25(OH) D 12-19 ng/mL) Deficient - (25(OH) D <12 ng/mL)	 18 (37.74 %) 15 (28.3 %) 20 (33.96 %)
Serum calcium (mg/dl)	8.37 ± 0.33
Serum phosphate (mg/dl)	3.64 ± 0.7
Serum Alkaline Phosphatase (U/L)	237.45 ± 44.36

Table 2. Comparison of biochemical profile, severity of asthma and parameters of exacerbation pre- and post-vitamin D treatment in vitamin D deficient asthmatic children (n=20)

Parameter	**Pre vitamin D treatment**	**Post Vitamin D treatment (At end of the study)**	**P value**
Vitamin D value (ng/ml)	9.91 ± 1.25	26.57 ± 3.97	<.0001
Serum Calcium (mg/dl)	8.37 ± 0.33	9.66 ± 0.73	<.0001
Serum Phosphate (mg/dl)	3.64 ± 0.7	4.66 ± 0.46	<.0001
Serum Alkaline Phosphatase Level (U/L)	237.45 ±44.36	153.25 ± 27.07	<.0001
Use of rescuer therapy per month	4.3 ± 1.53	1.7 ± 0.86	<.0001
Number of emergency hospital visits per month	0.24 ± 0.07	0.06 ± 0.06	0.0001

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Number of Hospital admissions per month; n	0.1 ± 0.07	0.04 ± 0.06	0.002
Daily dose of inhaled corticosteroids (µgm/day)	415 ± 138.7	245 ± 99.87	0.0001
Forced Expiratory volume, FEV 1 (L)	0.95 ± 0.13	1.17 ± 0.11	<.0001

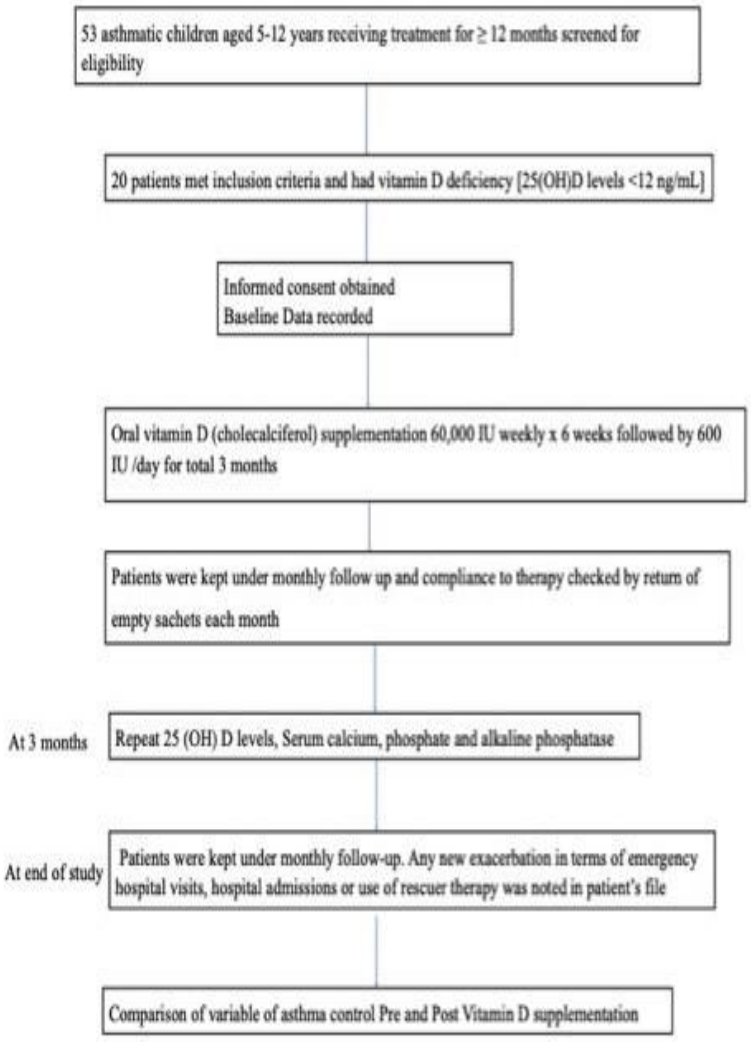

Fig.1

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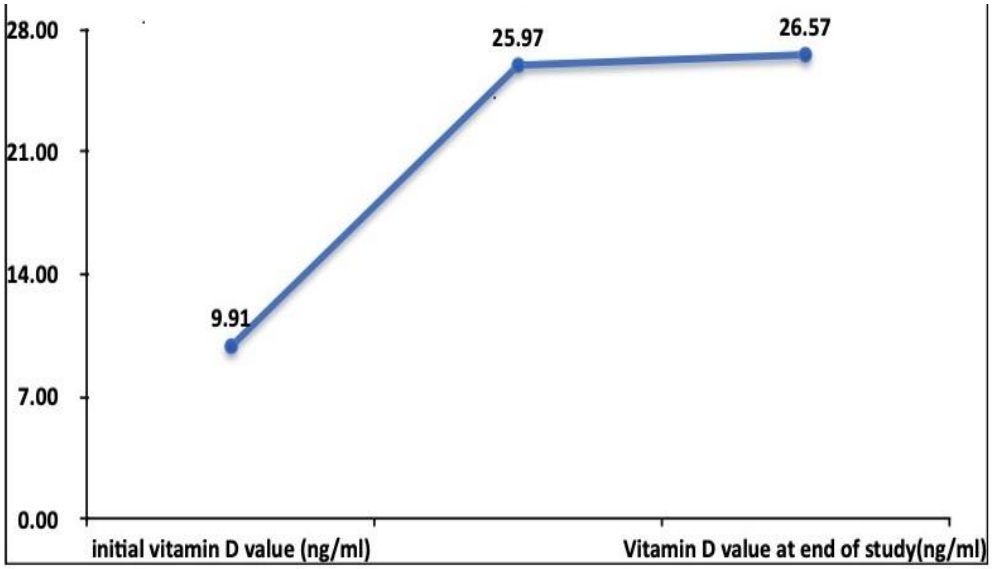

Fig. 2

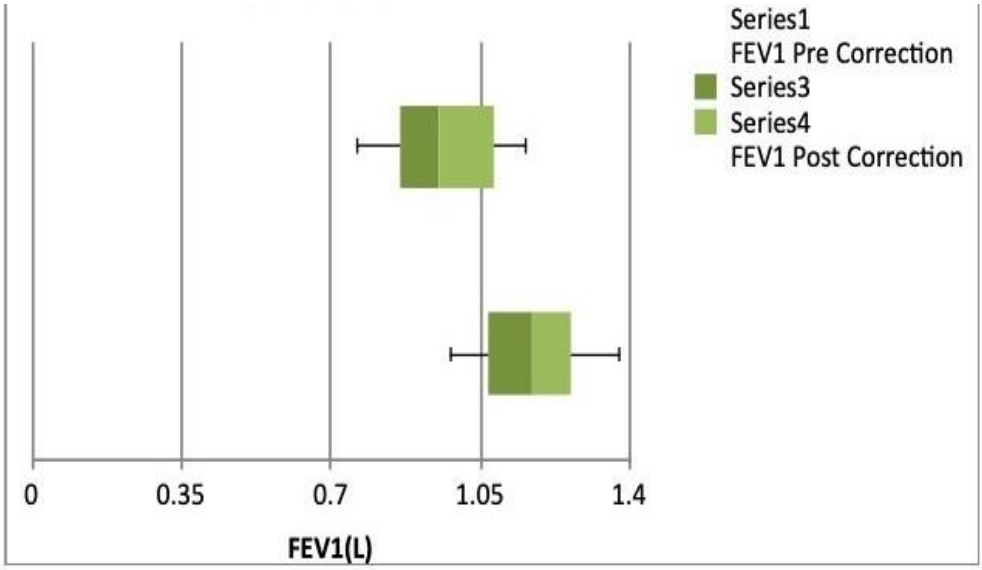

Fig.3

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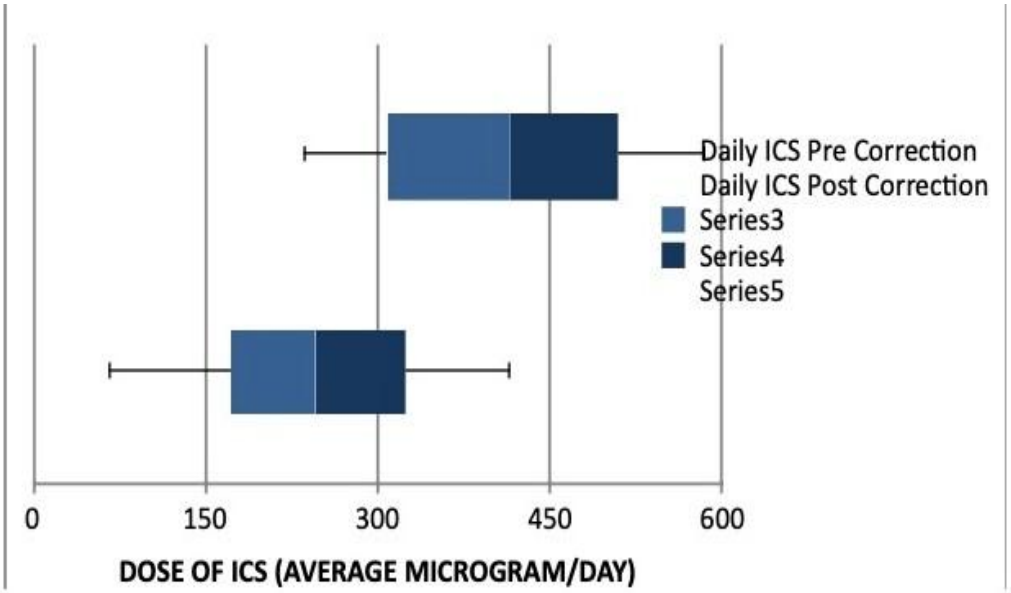

Fig.4

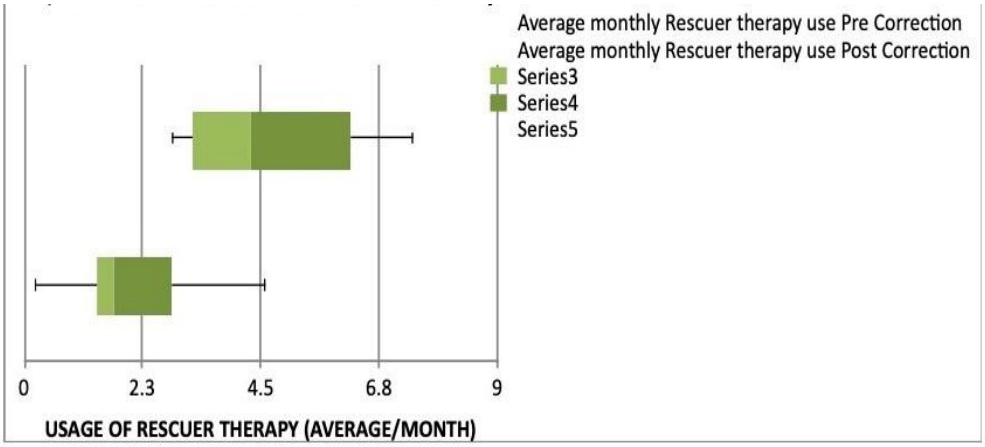

Fig.5