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EFFECT OF SELENIUM SUPPLIMENTATION IN BRONCHIAL ASTHMA IN CHILDREN IN THE AGEGROUP OF 1-12 YEARS

Pediatrics

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ABSTRACT

DESIGN: RANDOMISED CONTROLLED TRIAL
SETTINGS: TERTIARY CARE HOSPITAL
METHOD-
PATIENTS: Children of age group between 1-12 years attending OPD/IPD with symptoms of asthma, having recurrent wheeze (more than 2 episodes in 1 year) were included in study.
INTERVENTION: Patients were randomized in 2 groups i.e. cases and controls. One group (cases) has received Selenium supplementation according to RDA for respective age of patient for duration of 6 month along with their ongoing management for asthma. Second group (controls) received Placebo for duration of 6 month along with their ongoing management for asthma.
MAIN OUTCOME MEASURE(S): History of symptoms and treatment was documented in every 15 days interval. Anthropometric measurements were recorded in every 3 month interval up to 6 months.
RESULTS: It was observed that there was significant improvement in grade of asthma in 9 (21.4%) patients of Se group as compared to 2 (4.8%) patients in control group(p value=<0.05). There was significant reduction in number of wheezing episodes in Se group. 22(52.38%) patients in Se group had less than 5 episodes in 6 month period as compared to 8(19.05%) in control group. The difference in number of hospitalizations required in Se group was significantly less(p=<0.05) as compared to control group. There after 6 month follow up which is Statistically significant improvement in grade of PEM was seen in Se group as compared to control group(p value <0.05).
OBJECTIVE: Primary objective was to Study Effect of selenium supplementation in bronchial asthma in children of age group 1-12 years. Secondary objective was to study the effect of selenium supplementation on growth in asthmatic children.
CONCLUSIONS:- Selenium supplementation as per RDA is beneficial in improving symptomatology of asthma, nutritional status and hence quality of life of asthmatic patients in pediatric age group.

KEYWORDS

INTRODUCTION-

Selenium is a trace element that is naturally present in many foods such as cereals, grains, meat etc. and is used as a dietary supplement. SELENIUM (Se) is an essential micronutrient that is important for various aspects of human health, including optimal immune responses[1].

To date, 25 human selenoproteins have been identified. Selenoproteins have been characterized as an important antioxidant enzymes which includes glutathione peroxidase (GPX)-1, GPX-4, thioredoxin reductase-1, thioredoxin reductase-2, and selenoproteins P (SelP). Roles may be elucidated for other selenoproteins in reducing the oxidative stress or pathology of diseases like asthma[1,2,3].

It is well established that dietary selenium is important for a healthy immune response. The effects of Se deficiency can include reduced T-cell counts, impaired lymphocyte proliferation and responsiveness. Dietary supplementation of selenium in humans enhances the immune responses[1].

Bronchial asthma, the most common chronic disease of childhood, is defined as a chronic inflammatory disease of the airways, leading to symptoms of recurrent wheezing and cough. Asthma is characterized by a pro-oxidant pulmonary environment and allergen challenge in the lung which induces rapid increase in the oxidized to reduced glutathione ratio as well as ROS levels that precede inflammatory cell infiltration. It is found that deficiency of selenium plays an important role in the development of asthma. Some studies suggests that selenium supplementation for people with chronic asthma may help to improve symptoms[(2,15)].

Intake of selenium could suppress asthma inflammation by optimizing the activity of antioxidant selenoenzymes such as glutathione peroxidase (Gpx). This enzyme catalyzes reduction of hydrogen peroxide, lipid and phospholipid hydroperoxides by the antioxidant glutathione in airway epithelial lining. Glutathione is thought to play a role in defence against oxidative stress in asthmatic airways[1,2,3]. Furthermore, selenium supplementation, by increasing GPx activity and decreasing oxidative stress, inhibits the activity of nuclear factor-kB, a key transcription factor which drives inflammatory process in asthma[2].

Growth is a complex mechanism involving the multiplication of cells in various specialized tissues and systems**.** It is influenced by genetic, biological and environmental factors, and the harmony between them determines its more or less satisfactory conclusion[(4,5)].

Number of children having allergic disease like bronchial asthma were presented with growth arrest manifested initially by weight loss and that if the symptoms persisted, their height and bone maturity could be affected.

Selenium is an integral component of metabolic system essential for normal cell metabolism. Selenium is an integral part of various metabolic enzymes like thioredoxinreductase and various antioxidant enzymes which modifies human metabolism. These are associated with normal human growth .Hence in this study we observed effect of selenium supplementation on growth of asthmatic children.

METHODS-

The study was a randomized, single blind, placebo controlled trial (parallel group) done in Tertiary care setup at Government Medical College and Hospital, Aurangabad (MS) India from January 2015 to August 2016. We studied effect of selenium supplementation (within limits of RDA)[6,7] on health of asthmatic children by assessing change in symptoms, growth and quality of life as symptom free healthy life. Approval from Institutional ethical committee was obtained. Informed written consent was taken from parents of the selected children for participation in study.

Selection of study population:-

Inclusion Criteria

1. Children of age group between 1-5 years attending OPD/IPD With symptoms of asthma having Recurrent wheeze (more than 2 episodes in 1year).
2. Children of age group between 5-12 years attending OPD/IPD With symptoms of asthma having Recurrent wheeze (more than 2 episodes in 1year) and with 15% improvement of peak expiratory flow rate(PEFR) after inhalation of bronchodilator.

Exclusion Criteria:

1. Children having clinical evidence of any heart disease, renal or hepatic insufficiency or any MAJOR systemic disease.

GROUP	Grade	Frequency	Night symptoms with disturbed sleep
I	Intermittent (I)	Less than twice a week Brief exacerbation	Less than twice a month
II	Mild persistent (II)	More than once a week but less than once a day	More than twice a month
	Moderate persistent (III)	Once a day	Once a week
	Severe persistent (IV)	Continuous	Frequent

Sample size:
Sample size was calculated by using software OpenEpi version 3; considering power of study 80%,ratio of exposed to unexposed 1, odds ratio 9, risk/prevalence ratio 6.4 sample size was came to be 39 in each group(total subjects=78).

To increase sensitivity & credibility of study we enrolled 42 patients in each Se (Selenium supplemented) group and control group (total subjects=84). 108 children of 1 to 12 year age, admitted in the pediatric ward or attending OPD, who met inclusion criteria were included. Out of 108 patients 24 were excluded from study due to inability to complete follow up or non-compliance. Total 84 patients who completed 6 month of study period with follow up were included.

Information of age, sex, height and weight was recorded. The exact age of the child was computed from the child's date of birth. When data on the exact date of birth was not available, the age as told by mother to nearest month was used. Details regarding duration of illness, severity of illness (number of episodes in last year ,number of hospitalisations, ongoing medication), family history were noted at the time of enrolment.

For children of age group in between 5-12 years PEFR was measured by using MINI-WRITE PEAK FLOW METER. Diagnosis of asthma was done by performing bronchodilator reversibility test [8,9].
For this study patients were graded into 2 groups as follows [8]:-

Weight and height were recorded at 3 month interval. PEM was graded according to weight for age and IAP classification of PEM [10]. Height was graded according to WHO and IAP growth charts for respective age [10,11].

Randomization:
Alternate subjects were selected and allotted either Se (selenium supplemented) or control group for purpose of randomization so as patients were equally distributed.

This was a single blinded study. Patient's caretaker were kept unaware regarding there group and medication.

Intervention:
Se (Selenium supplemented) group received selenium supplementation in form of crushed tablets in single daily dose for 6 months. It was given within range of RECOMMANDED DAILY ALLOWANCE[6,7] for respective age group as given in table below; and control group received crushed placebo tablets for period of 6 months.

Recommended Dietary Allowances (RDAs) for Selenium				
Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	15 µcg	15 µcg		
7–12 months	20 µcg	20 µcg		
1–3 years	20 µcg	20 µcg		
4–8 years	30 µcg	30 µcg		
9–13 years	40 µcg	40 µcg		
14–18 years	55 µcg	55 µcg	60 µcg	70 µcg
19–50 years	55 µcg	55 µcg	60 µcg	70 µcg
51+ years	55 µcg	55 µcg		

Monitoring & follow up:-
Every patient was followed at every 15 days interval. Details regarding number of wheezing episodes, any required treatment for that, number of hospitalization episode were noted and graded.

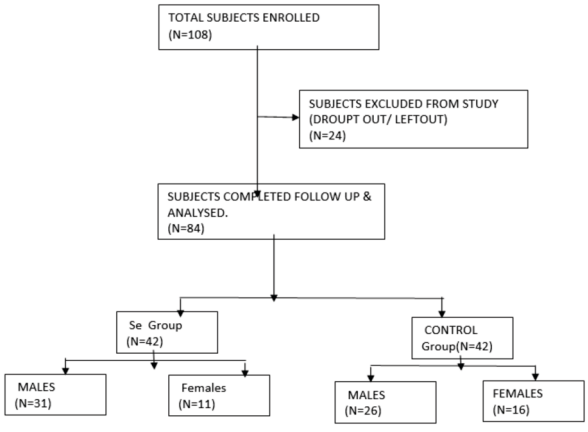
Anthropometric measurements were recorded at every 3 month interval i.e. height and weight for period of 6 month.

All patients were followed up to 6 months. Patients who did not complete follow up were excluded from study. All enrolled patients were analysed for improvement of symptomatology of asthma, improvement in grade of PEM as per IAP classification and quality of life.

Statistical analysis
Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Data were tested first for normal distribution by Klomogorov– Smirnov test. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc.,Chicago, IL, USA) version 21.

RESULTS-

Flowchart showing enrolment details.



108 children of 1 to 12 year age, admitted in the pediatric ward or attending OPD, who met inclusion criteria were included. Out of 108 patients 24 were excluded from study due to inability to complete follow up or non-compliance. Total 84 patients who completed 6 month of study period with follow up were included. There were 42 patients in Se and control group each.

Table No. 1

Asthma Grade	Se Group	Control Group
No Change	31 (73.81%)	33 (78.57%)
Improved	9 (21.43%)	2 (4.76%)
Deteriorated	2 (4.76%)	7 (16.67%)
Total	42 (100.0%)	42 (100.0%)
	p- value - 0.026	

It was observed that there was improvement in grade of asthma in 9 (21.4%) patients of Se group as compared to 2 (4.8%) patients of control group. There was deterioration in 2 (4.76%) patients of Se group as compared to 7 (16.67%) in controls. This change in grade of asthma in patients was statistically significant(p value=<0.05)(table No. 1).

TABLE NO. 2 –
Table showing total number of wheezing episodes during study period

No. of Episodes in 6 months of treatment	Group	
	Se Group	Control Group
< 5	22 (52.38%)	8 (19.05%)
6 to 10	11 (26.19%)	13 (30.95%)

11 to 15	4 (9.52%)	8 (19.05%)
> 15	5 (11.90%)	13 (30.95%)
Total	42 (100.0%)	42 (100.0%)
P value	0.01	

It was observed that in Se group, 22 (52.38%) subjects had less than 5 episodes in 6 month period. Similarly 11 (26.19%) subjects had 6 to 10 episodes, 4 (9.52%) subjects had 11 to 15 episodes and 5 (11.90%) subjects had more than 15 episodes. On other side in control group, 8 (19.05%) subjects had less than 5 episodes in 6 month period. Similarly 13 (30.95%) subjects had 6 to 10 episodes, 8 (19.05%) subjects had 11 to 15 episodes and 13 (30.95%) subjects had more than 15 episodes. The difference in number of wheezing episodes in Se group as compared to controls was statistically significant i.e. p value is <0.05(table No.-2).

Table No.3.Table showing total number hospitalization during study period

Total number of Hospitalization episodes	**Group**		**Total**
	Se Group	**Control Group**	
None	30 (71.43%)	14 (33.3%)	43 (51.2%)
1	7 (16.67%)	14 (33.3%)	21 (25.0%)
2	4 (9.52%)	11 (26.2%)	15 (17.9%)
3	1 (2.38%)	3 (7.1%)	4 (4.8%)
Total	42 (100.0%)	42 (100.0%)	84 (100.0%)
P value	0.01		-

In Se group 29 patients required no hospitalization as compared to 14 i.e.33.3% from control group. Similarly number of hospitalizations were less in patients of Se group as compared to controls which is statistically significant (p value <0.05)(table No.3).

Table No.4-Table showing change in grade of PEM in cases after 6 month follow up

PEM	**Se group**		**Control group**	
	On day 1	**At end of 6 month**	**On day 1**	**At end of 6 month**
No Malnutrition	19 (45.24%)	30 (71.44%)	22 (52.38%)	22 (52.38%)
Grade I	16 (38.10%)	6 (14.29%)	12 (28.57%)	10 (23.81%)
Grade II	2 (4.76%)	4 (9.52%)	7 (16.66%)	9 (21.43%)
Grade III	5 (11.90%)	2 (4.76%)	1 (2.38%)	1 (2.38%)
Total	42 (100.0%)	42 (100.0%)	42 (100.0%)	42 (100.0%)
p- value	0.029		0.933	

There was improvement in grade of PEM after 6 month follow up in Se group which is statistically significant (p value <0.05)(Table No.4).

Table No.5- Table showing change in Height in cases after 6 month follow up

Height	Se		Control	
	Day		Day	
	Day 1	6 months	Day 1	6 months
Above mean	3	5	4	3
	7.1%	11.9%	9.5%	7.1%
Mean to -1SD	12	12	14	15
	28.6%	28.6%	33.3%	35.7%
-1 SD to -2 SD	11	14	7	7
	26.2%	33.3%	16.7%	16.7%
-2 SD to -3 SD	9	7	9	9
	21.4%	16.7%	21.4%	21.4%
< -3 SD	5	4	8	8
	11.9%	9.5%	19.0%	19.0%
Total	42	42	42	42
	100.0%	100.0%	100.0%	100.0%
P value	>0.05		>0.05	

Table No.5 show no significant change in distribution of height among both groups i.e. p value >0.05 after 6 month follow up.

DISCUSSION-

Bronchial asthma, the most common chronic disease of childhood, is defined as a chronic inflammatory disease of the airways, leading to symptoms of recurrent wheezing and cough.Asthma lowers quality of life and significantly adds economic burden directly or indirectly; especially missed school days for children and missed work days for adults. Severity of asthma and poor quality of life runs side by side [12].

Nevin uzner et. al 2001 [13] studied serum selenium levels in bronchial asthma said- there is an oxidative stress in bronchial asthma, and antioxidant capacity decreases in parallel to a decrease in serum selenium and zinc levels. This leads to a further increase in oxidative stress and as a result, inflammation and hyper-reactivity.

Seif O Shaheen et al. [14] done Randomized, double blind, placebo-controlled trial of selenium supplementation in adult asthma in 2007. 197 participants were randomized to receive either a high-selenium yeast preparation (100 µg daily, n = 99) or placebo (yeast only, n = 98) for 24 weeks. The primary outcome was asthma-related quality of life (QoL)score. Secondary outcomes were mean morning and evening asthma symptom scores, waking at night due to asthma symptoms and increased bronchodilator usage.

The QoL score improved more in the active treatment group than in the placebo group,but the difference in change in score between the two groups was not statistically significant (p = 0.47). Hence they concluded that Selenium supplementation was not associated with any significant improvement in quality of life of patients of bronchial asthma.

Mohamed Farouk Allamet.al [15] systematically examined RCTs that evaluated the role of selenium supplementation in chronic asthma. They could localize only one RCT (Hasselmark 1993). No other RCT intended to assess the value of selenium supplementation in chronic asthma since then.

In study done by hasselmark [16], total of 24 patients (12 in each group) suffering from intrinsic asthma (14 men, 10 women) with age ranged between 18 and 75 years were selected for the study. 100mcg sodium selenite and placebo was given to selenium group & placebo group respectively. Intervention was done for 14 weeks. Outcome was measured by comparing various parameters i.e. Symptoms (in house scale), medication usage.

Randomized Controlled Trial by hasselmark 1993 [16] reported significant clinical improvement in the selenium supplemented group, as compared to placebo group. It showed improvement in 6 (50%) patients from selenium group and only 1 (0.83%) from placebo group. The improvement was in the form of decrease infrequency and severity of symptoms. The difference in distribution was statistically significant (P = 0.042).

We could not find any study in paediatric age group which was focused on role of selenium in bronchial asthma.

In present study at the end of 6 months, it showed improvement in grade of asthma among selenium group as compared to control group. It was observed that among selenium group 9 patient i.e.21.4% showed improvement in grade of asthma as compared to 2 patients i.e. 4% in control group. This improvement in selenium group was probably due to reduction in airway inflammation from antioxidant effect of selenium.

Present study also shows deterioration in 2 (4.76%) patients of selenium group as compared to 7 (16.67%) in controls which showed that there was less deterioration in selenium supplemented group as compared to control group. This difference in distribution of improvement and deterioration in these two groups was statistically significant (p value- <0.05).

Deterioration was more in control group which was probably due to continued airway inflammation and remodelling.

Deterioration in some patient of selenium supplemented group could be due to non-responsiveness to ongoing inhalational corticosteroids and selenium supplementation or increased free oxygen radical load in airway.

In present study it was observed that number of wheezing episodes were less among selenium group as compared to control group .The difference in wheezing episodes in selenium group and control group was statistically significant (p value is <0.05). Decrease in number of wheezing episodes in selenium supplemented group offered better quality of life to asthma patients. Probable reason behind decrease in number of wheezing episode is reduction in oxidative stress in airway which lead to decrease in disease severity.

In present study we also observed total number of hospitalizations during study period as parameter of improvement in asthma status of patients. It was observed that among selenium group 30 (71.43%) patients required no hospitalization as compared to 14 (33.3%) from control group. It was observed that 12 (28.57%) patients from selenium group required at least 1 hospitalization in 6 months study period as compared to 28 (66.67%) patients from control group. The difference number of hospitalizations in selenium group and control group was statistically significant (p value <0.05).

This decrease in number of hospitalization in selenium supplemented group was due to decrease in number of wheezing episodes and severity of wheezing episodes resulted in better quality of life.

In present study we observed that there was statistically significant improvement in grade of malnutrition hence weight gain in asthmatic children supplemented with selenium. Whereas there was no significant change in height.

The improvement in weight is perhaps due to improvement in grade of asthma, reduction in number of wheezing episodes hence improved quality of life. The improvement of overall immunological status due to Se supplementation may be additional benefit.

We could not find significant change in height perhaps due to less study period.

Though we found significant benefit in asthmatic children with Se supplementation, further research is needed to establish exact role of Se supplementation, the existence of Se deficiency in society and endemicity of Se deficiency.

LIMITATIONS-

We supplemented the study group without knowing pre-enrollment selenium status of the patients. Hence can't comment whether selenium effects were because of selenium deficiency correction or it's direct effect.

Similarly we can't comment whether improvement in grade of PEM is due to correction of deficiency of selenium or due to direct positive effect of selenium on body metabolism or due to improvement in asthma control hence improved appetite which indirectly improved grade of PEM.

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