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ORIGINAL RESEARCH

Role of Vitamin A in Measles complications: A study in Garhwal region of Uttarakhand

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ABSTRACT

Background: Measles is a highly communicable viral infection with serious complications.There have been continued outbreak of measles in countries and it has more than 90% of secondary attack rate.It has been observed that Vitamin A deficiency is a recognised risk factor for severe measles infection.Therefore we conducted this study to see association between measles and Vitamin A. **Objective:** Measurement of vitamin A level in measles patient and to find out its association with measles. **Methods:** This is a prospective descriptive study.Children presented to pediatric OPD/IPD with high grade fever and rash typical of measles that started behind ear enrolled in study. **Result**: A total of 109 IgM positivemeasles, 34 patients were admitted with complications of measles which accounted for 31.19% of total confirmed cases of measles and 9.9 % of clinical measles.Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 30 (88.2%) were low. In line with the hypothesis of this study, children with complicated measles are associated with lower levels of vitamin A levels. **Conclusion:** In our study Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 30 (88.2%) were low. This was in line with the hypothesis of this study; children with complicated measles are associated with lower levels of vitamin A levels.It was seen that children with low levels were more likely -to have a fever at a temperature of 40°C or higher (78% vs 41%), to have a fever for 7 days or more (51% vs 25%), to get hospitalized (56% vs 32%).

Keywords: Role of Vitamin A, Measles, complications

INTRODUCTION

Measles is a contagious vaccine-preventable illness caused by the measles virus, a paramyxovirus of the genus Morbillivirus.(1) Usually, it is a mild illness but in children with risk factors such as malnutrition, overcrowding, etc. the disease progress to complicated and severe complicated measles. Being a highly contagious disease measles has a secondary attack rate of more than 90% in susceptible individuals with high case fatality rates.(2)

Globally about 39.9 million cases of measles occur every year out ofwhich 777,000 deaths occur due to measles.The majority (more than 95%) of measles deaths occur in countries with low per capita incomes and weak health infrastructures.The World Health Organization regions of Africa and Southeast Asia had 70% of incident cases and 84% of measles-related deaths; 11 countries alone (Afghanistan, Burkina Faso, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Niger, Nigeria, Pakistan, Somalia, Uganda) account for 66% of deaths.(3)India reported 17,250 measles cases in 2016.(4)

The risk of serious measles complications is higher in infants and adults. These include Otitis media (7–9%), pneumonia (1–6%), diarrhea (6%), blindness, and post-infectious encephalitis (1 per 1000 cases).(5)Sub acute sclerosing pan-encephalitis is one of the serious complication of measles (1 per 100 000 cases).One out of 20 children gets Pneumonia and 1 out of 1000 gets encephalitis.Mean case fatality rate in India was 2.5%.

In countries with poor vaccination coverage, nearly all children get measles by 5 years of age. Currently, measles is a disease of older children and adults in which primary vaccination has failed.(6)The measles vaccine has been in use since the 1960s. WHO

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recommends immunization for all susceptible children and adults for whom measles vaccination is not contraindicated.

In India, due to the introduction of the second measles dosage in the National Immunization Programme in 2010 and good surveillance activities, the measles specific mortality rates have fallen by 51 % between 2010 and 2015.(7)The world summit of children has set a goal of a 90% reduction of measles cases and a 95% reduction of measles deaths.(8)

The World Health Organization (WHO) recommends the administration of an oral dose of vitamin A (200,000 international units (IU), or 100,000 IU in infants) each day for two days to children with measles when they live in areas where vitamin A deficiencymay be present.There is anoverall significant reduction in mortality with vitamin A therapy for children with measles i.e. two doses were associated with a reduced risk of mortality and pneumonia-specific mortality in children under the age of two years.(9)

In countries e.g. USA, vitamin A deficiency is associated with an increased risk of admission to hospital and severe disease.Previous researchers couldn't find evidence that a single dose of 200,000 IU of vitamin A per day was associated with reduced mortality among children diagnosed with measles.(10)

There is a paucity of Indian studies on this topic of research of vitamin A supplementation and protective efficacy. A systemic review conducted by D'Souza et al. found that there were not enough studies to separate the individual effects of age, dose, formulation, hospitalization, and case fatality in the study area. They concluded that 200 000 IU of vitamin A repeated on 2 days should be used for the treatment of measles as recommended by WHO in children admitted to hospitals in areas where the case fatality is high.(11)Low vaccine coverage rate with low vaccine efficacy leads to a higher rate of complications and hospitalization.(12)In this study we will study the association of vitamin A supplementation with measles-related complications and case fatalityrate to studythe mean vitamin A levels in complication of measles.

Hence this study was taken to identify the relation of the level of vitamin A and case fatality in measles and to identify the relation/prediction of vitamin A levels to the respective complication of measles.

MATERIAL AND METHODS

This Prospective descriptive study was conducted Pediatric Ward and Pediatric OPD. Duration of study was one year (December 2020 to December 2021)

The standard case definitionof the **CDC** was used as a diagnostic of measles.

A combination of major and minor criteria was used to clinically identify the measles cases;

Major criteria:

1. A child with high fever (more than101 degree Celsius) for 3 days or more and
2. Characteristic rashes that started behind the ears. Starting at hairline

Minor criteria:

Presence of 1.Cough; 2.Coryza or 3.Conjunctivitis

A study subject was considered to have measles if the case presented with one of the major criteria and any ofthe three minor criteria.

Sample size: All the children diagnosed to have measles with the above clinical criterion of CDC age 6 months -14 years seen in OPD or hospitalized to the pediatric ward will be included in the study. Thus sample size calculation is not required.

Sampling technique: Not applicable.

INCLUSION CRITERIA

A combination of major and minor criteria was used to clinically identify the measles cases(45)

Major criteria:

1. A child with high fever (more than 101 degree Celsius) for 3 days or more and
2. Characteristic rashes that started behind the ears starting at the hairline.

Minor criteria:

Presence of 1.Cough; 2.Coryza or 3.Conjunctivitis

A study subject was considered to have measles if the case presented with one of the major criteria and any ofthe three minor criteria.

EXCLUSION CRITERIA

1. Uncomplicated measles.
2. Incomplete data.
3. Patient readmitted.

STATISTICAL ANALYSIS

The data will be analyzed and interpreted by using descriptive and inferential statistics and will be represented in form of tables, diagrams, and graphs, etc. by the investigator.Data will beanalyzed by using SPSS version 10 for windows.

RESULTS

A total of 109 IgM positivemeasles, 34 patients were admitted with complications of measles which accounted for 31.19% of total confirmed cases of measles and 9.9 % of clinical measles.

Vaccination status and measles complications

48% received the measles vaccine at 9 months, 94% received the MR vaccine and 67% received 1 or more dosage of measles/MR at the encounter.

Exposure to the indexed case

Confirmed exposure to the indexed case was found in 4.23 % of clinically diagnosed measles, 7.33 % of confirmed measles, and 23.8% in complicated measles.

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Clinical features of confirmed and complicated measles

Most common clinical feature besides fever and rash (n= 100%) were found as rhinorrhoea (n=77.0 , 70.6 %) followed by vomiting (n=42 , 15.7 %) and cough (n= 26 , 9.73%)

Investigations

Abnormal chest X-ray, lymphocytosis, and anemia for age were more common in complicated measles compared to confirmed measles and were significant for developing complicated measles (p <0.05%).

The percentage of measles patients who developed pneumonia did not differ significantly regarding sex (p = 0·9485) but it did differ significantly in the age groups (p< 0·001).

Complications

Most common complication of confirmed measles was pneumonia in 94.11% (n= 32) followed by diarrhoea in 32.35 % (n= 11). 14.70 % of children (n=5) presented with deep and extensive mouth ulcers.

Vitamin A levels

Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 30 (88.2%) were low. In line with the hypothesis of this study, children with complicated measles are associated with lower levels of vitamin A levels.

Children with low levels were more likely

- to have a fever at a temperature of 40°C or higher (78% vs 41%)
- to have a fever for 7 days or more (51% vs 25%)
- to get hospitalized (56% vs 32%)
- to have pneumonia and diarrhoea (p-value < 0.05).

In our study, a total number of 337 patients of pediatric age group were screened for measles out of which 109 patients were measles IgM positive by ELISA. The rest ofthe patients were false positive.

A total of 109 IgM positivemeasles, 34 patients were admitted with complications of measles which accounted for 31.19% of total confirmed cases of measles and 9.9 % of clinical measles.No mortality secondary to measles was observed in the study population.The average age of a child with Complicated measles was 15.8 months with males to the female distribution of 2.1:1 with a peak incidence in the age group 12-23 months (n=22, 65%).

Vaccination status

48% received the measles vaccine at 9 months, 94% received the MR vaccine and 67% received 1 or more dosage of measles/MR at the encounter.

Table 1: Clinical features of confirmed measles

Clinical features	Number of confirmed measles (n= 109)	Percentage of all confirmed cases
Rhinorrrhoea	77.0	28.83%
Cough	26	9.73%
Vomiting	42	15.7%
Diarrhoea	34	12.73%
Conjunctivitis	9	3.37%
Koplik spots	21.0	7.86 %
Mouth ulcer	12	4.49 %
Dyspnoea	22	8.24 %
Sore throat	16	5.99 %
Prurulent eye discharge	8	2.99 %

Most common clinical feature besides fever and rash (n= 100%) werefound as rhinorrhoea (n=77.0 , 70.6 %) followed by vomiting (n=42, 15.7 %) and cough (n= 26 , 9.73%)

Investigations

Table no. 2showing investigations done in confirmedcases

	Confirmed cases N	Confirmed cases %
Anemia for age	17	15.59 %
Leucopenia	51	46.79%
Lymphocytosis	43	39.44 %
Abnormal Chest X-ray	2	1.83 %

Infants had a lower risk than children >12 months of developing lymphopenia (OR, 0.029, 95% CI, 0.003–0.244) and conjunctivitis (OR 0.294, 95% CI 0.103–0.843) but a higher risk of developing diarrhea (OR 3.248, 95% CI 1.125–9.379)

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Complications

Out of clinically diagnosed cases of measles, 31.19 % of children developed complications

Most common complication of confirmed measles were pneumonia in 94.11% (n= 32) followed by diarrhoea in 32.35 % (n= 11).

Table no. 3 showing complicationsin confirmed cases of measles(n=34).

	No. Of complicated measles	percentage
Pneumonia	32	51.61 %
Diarrhea	11	17.72 %
Febrile seizures	1	1.61 %
Dysentery	3	4.83 %
Encephalitis	2	3.22%
Croup	1	1.61 %
Otitis media	1	1.61 %
Stomatitis	5	8.06 %
SSPE	Nil	Nil
Sinusitis	1	1.61 %
Sepsis	4	6.45 %
Pharyngitis	1	1.61 %
Clouding of cornea	1	1.61 %

Vitamin A levels

Table 4: showing vitamin A level in complicated cases of measles on the day of encounter

Complications	Mean Vitamin A level(HPLC)
Pneumonia	0.03 mg/L
Diarrhea	0.08 mg/L
Febrile seizures	0.10 mg/L
Dysentery	0.14 mg/L
Encephalitis	0.01 mg/L
Croup	0.12 mg/L
Otitis media	0.13 mg/L
Stomatitis	0.10 mg/L
SSPE	0.01 mg/L
Sinusitis	0.19 mg/L
Sepsis	0.17 mg/L
Pharyngitis	0.10 mg/L

Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 30 (88.2%) were low. Children with low levels were more likely to have a fever at a temperature of 40°C or higher (78% vs 41%), to have a fever for 7 days or more (51% vs 25%), and to be hospitalized (56% vs 32%) and to have pneumonia and diarrhea (p-value < 0.05).

Patients with complicated measles did not received Routine vitamin A supplementation in the last 6 months beforethe presentation. And therapeutic vitamin A supplementation could not be provided due to poor government medicine supply.

DISCUSSION

Measles is a contagious vaccine-preventable illness but a mild illness but in children with risk factors such as malnutrition, overcrowding, etc. the disease progress to complicated and severe complicated measles. The increase in immunization coverage and the introduction of 2 dosages of measles vaccine have led to a change in the epidemiology of measles.

Considering the background knowledge and lacunae in the existing literature and contrasting information related to the association between measles-related complications and vitamin A supplementation, the current study will be testing the association between vitamin A supplementation in the prevention of measles-related complications and measles-related fatality in the era of measles eradication.

With this current study, an attempt will be made to study the possible association of vitamin A supplementation with measles-related complications and case fatality in the era of the verge of eradication in the Garhwal region of Uttrakhand.

In our study,a total of 109 IgM positivemeasles were found during the study period. Out of these 109 patients,34 patients were admitted to the wards with complications of measles which accounted for 31.19% of total confirmed cases of measles and 9.9 % of clinical measles.

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Vaccination status and complicated measles

We found that there was a positive correlation between the lack of vaccination and the development of complications($p< 0.05$).48% received the measles vaccine at 9 months, 94% received the MR vaccine and 67% received 1 or more dosage of measles/MR at the encounter.

A similar lack of vaccination status in complicated measles was seen by a study by Vemula et al who found that the majority (89.7%) had not received measles, mumps, and rubella (MMR) vaccination and 10.3% had only 1 dose.(13) Similar conclusions were drawn by Marafu et al who found that the risk of complications was higher in unvaccinated cases and vaccination was protective against the occurrence of complications.(14)

Similar to our study,an Indian study by Bhatt et al who found a positive correlation between lack of immunization and development of complications.(15)

Zahidie et al in their study found that measles cases were also more likely to have never received any vaccination [AOR: 10.1 (4.5 - 22.5)] and having no other children vaccinated at home [AOR: 3 (1.5 - 5.3)].(16)

Literature has already revealed that Measles vaccination was highly associated with low risk for Measles [OR: 0.14 (0.13 - 0.16)].(17)

Exposure to the indexed case

Confirmed exposure to the indexed case was found in 4.23 % of clinically diagnosed measles, 7.33 % of confirmed measles, and 23.8% in complicated measles.

Complications

In our study out of clinically diagnosed cases of measles 31.19 % of children developed complications. A total of 62 complications were noticed in 34 patients. Some of the patients had more than one complication of measles.

90.9 % of all 34 patients showed one or more general danger signs at the time of presentation.

Table 5: showing a Comparision of various complications of measles and mortality observed in various studies:

Complications	Our study	Samsi et al (18)	Rashid et al (19)	Li et al (20)	Khan et al (21)	Bhatt et al (22)	Hussain et al (23)
Pneumonia	51.61%	94.4%	68%	100%	56.29%	57.44 %	29.41 %
Diarrhoea	17.72%	25.9%	31%	Nil	17.22%	12.8%	26.47 %
Otitis media	1.61%	Nil	Nil	Nil	2.98%	4.25 %	7.35 %
Stomatitis	8.06%	Nil	Nil	nil	2.34%	Nil	20.58 %
Eye lesions	1.61%	Nil	31%	Nil	Nil	Nil	2.94%
Encephalitis	3.22%	88.9%	Nil	Nil	7.28%	2.13 %	2.94%
Myocarditis	Nil	Nil	Nil	Nil	Nil	Nil	2.94 %
Tonsillitis	1.61%	Nil	Nil	Nil	Nil	2.13 %	Nil
UTI	Nil	Nil	Nil	Nil	Nil	2.13 %	Nil
Febrile convulsions	1.61%	Nil	Nil	Nil	6.95%	4.25 %	Nil
Dysentery	4.83%	Nil	Nil	nil	0.99%	Nil	Nil
Emphysema	Nil	Nil	Nil	Nil	1.32%	Nil	Nil
Croup	1.61%	Nil	Nil	Nil	3.31%	Nil	Nil
pneumothorax	Nil	Nil	Nil	Nil	0.66%	Nil	Nil

Abnormal chest X-ray, lymphocytosis, and anemia for age were more common in complicated measles compared to confirmed measles and were significant for developing complicated measles ($p <0.05\%$).

Infants had a lower risk than children >12 months of developing lymphopenia (OR, 0.029, 95% CI, 0.003–0.244) and conjunctivitis (OR 0.294, 95% CI 0.103–0.843) but a higher risk of developing diarrhea (OR 3.248, 95% CI 1.125–9.379).Similar results were seen by a study of Vemula et al.(24)

In our study, the percentage of measles patients who developed pneumonia did not differ significantly regarding sex ($p = 0{\cdot}9485$) but it did differ significantly in the age groups ($p< 0{\cdot}001$).

Vitamin A levels and complicated measles

In our study Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 30 (88.2%) were low. This was in line with the hypothesis of this study; children with complicated measles are associated with lower levels of vitamin A levels.

Also, in our study it was seen that children with low levels were more likely -to have a fever at a temperature of 40°C or higher (78% vs 41%), to have a fever for 7 days or more (51% vs 25%), to get hospitalized (56% vs 32%). This was similar to a study by Frieden et al who found that Children with low levels were more likely to have a fever (68% vs 44%), to have a fever for 7 days or more (54% vs 23%), and to be hospitalized (55% vs 30%). Children with low vitamin A levels had lower measles-specific antibody levels.(25)

Similar to our study Butler et al found that children with measles in an urban United States community, retinol concentrations were depressed, and the degree of depression was associated with illness severity.

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Retinol concentrations ranged from 0.25 to 1.18 mumol/L (median 0.58 mumol/L); 82 (72%) patients had low retinol concentration (< or = 0.70 mumol/L). Median retinol concentrations were lower among hospitalized patients (0.56 vs 0.70, P = .006) and patients with pneumonia (0.52 vs 0.64, P = .02) but higher among children with otitis media (0.63 vs 0.54, P = .01).(26)

Varavithya et al in their study found that Thirty-two percent of the measles patients had serum vitamin A concentrations less than 10 micrograms/dl and concluded that Since measles and xerophthalmia have frequently been associated, vitamin A supplementation for measles patients is recommended particularly for malnourished children.(27)

CONCLUSIONS

There exists a positive correlation between lack of vaccination and the development of complications due to measles.

The most common clinical feature besides fever and rash are rhinorrhoea followed by vomiting and cough while

Abnormal chest X-ray, lymphocytosis, and anemia for age are more common in complicated measles compared to confirmed measles.

Vitamin A levels in children with measles ranged from 0.01-0.23 mg/L; 88.2% are low.

Children with low levels of vitamin A with measles were more likely

- to have a fever at a temperature of 40°C or higher
- to have a fever for 7 days or more
- to get hospitalized
- to have pneumonia and diarrhea

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