Sys Rev Pharm 2021;12(1):207-210
A multifaceted review journal in the field of pharmacy

THERAPEUTIC EFFECT OF VITAMIN A ON COVID-19 PATIENTS AND ITS PROPHYLACTIC EFFECT ON CONTACTS

Mahmood M. Al-Sumiadai[1], Hazim Ghazzay[2], Rafi Khaleel Al-Ani[3]

[1] DCH/ Ministry of Health- Anbar health directorate/ Ramadi city/ MOH/Iraq.

[2] F.I.C.M.S / Internal medicine/Department of medicine / Collage of medicine / university of Anbar/Iraq.
[3] CIB/ Ministry of Health- Anbar health directorate/Iraq
alsumaidaidrmah@gmail.com

ABSTRACT
Background: No other similar study was done on the role of vitamin A in the treatment of COVID-19.
Objective: To find the effect of vitamin A on patients with COVID-19 and its protective effect on contacts.
Patient and Methods: A cross-sectional study was done on two groups. The first group of 100 diagnosed mild to moderate patients with COVID-19, 50 patients received two doses of vitamin A (200,000 I.U.) for two days, another 50 patients received a placebo. Data about clinical features, SPO2, and the mean duration of symptoms collected after 24 and 48 hours from the administration, in addition to the number of patients who deteriorate their SPO2. A second group was contacted to patients diagnosed with COVID-19, part of them received two doses (200,000 I.U.) of vitamin A and others received a placebo. The comparison was between the percentage of getting the infection and the duration of symptoms among those who got the infection.
Results: A significant improvement in symptoms, shorter duration of illness, with a lower number of patients who deteriorate their SPO2 among patients given vitamin A compared to control. A lower incidence of infection among contacts who received vitamin A in comparison to contacts received placebo with shorter duration of symptoms among those who got the infection.
Conclusions; A great benefit of the use of vitamin A in patients with COVID-19 and to contacts. Adding vitamin, A to the protocol management of COVID-19 is recommended.

Keywords; COVID-19, Vitamin A, Therapy, Contacts, Prophylaxis.

Running title; Vitamin A in treatment of COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a beta coronavirus closely linked to the SARS virus. By way of definition, a symptomatic COVID-19 case is a person who has developed signs and symptoms suggestive of COVID-19.[1]

Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by mammals, thus it is an obligatory dietary factor. It is now well established that all vertebrates require vitamin A for adequate growth, cell and tissue differentiation, vision, development and function of the immune system, and survival.[2] Concentrations of preformed vitamin A are highest in liver and fish oils. Other sources of preformed vitamin A are milk and eggs, which also include some provitamin A. Most dietary provitamin A comes from leafy green vegetables, orange and yellow vegetables, tomato products, fruits, and some vegetable oils .[3]

The doses of vitamin A used in children with measles (100,000-200,000 IU) are given once or twice.[2] The recommended dose in children for more than one year and adults with xerophthalmia (vitamin A deficiency) is (200,000 IU) for two days. [4] Dosages of vitamin A in the order of 100 times the recommended daily allowance are required to produce toxicity in adults, and for this reason, acute toxicity is quite uncommon. Symptoms of acute toxicity include gastrointestinal upset and neurological symptoms of headaches, blurred vision, vertigo, and muscular incoordination.[5] Intakes of vitamin A greater than 10,000 IU per day are not recommended for well-nourished pregnant women.[6]

The mechanism of vitamin A on infections could be by enhancing the immune response by deferent ways, including; morphological formation of the epithelium, epithelial keratinization, and functional maturation of epithelial cells which are regarded as the first-line defense against pathogen invasion.[7,8] Regulate the apoptosis of thymocytes.[9-11] Induces T cell migration to the thymus where they developed into mature T cells.[12,13] Promoting T cell activation and T helper cell responses at minimal levels.[14] Lastly, the effect of vitamin A on B cell may by enhancing antibody production, [15,16] and regulating B cell activity.[17,18]

There are many applications of using vitamin A in the treatment of infectious diseases including;

1. Tuberculosis. A longitudinal cohort study of tuberculosis

showed that vitamin A deficiency is dose-dependently correlated to the occurrence of tuberculosis.[19-21]

2. Acquired Immune Deficiency Syndrome (AIDS). Vitamin A, vitamin C, and vitamin E are all-natural antioxidants, and by inhibiting the oxidative stress of the organism, it is postulated that these vitamins can ameliorate the progression of AIDS.[22,23]

3. Infectious diseases in children, vitamin A has demonstrated a therapeutic effect, to some extent, in diseases transmitted through the respiratory system, such as pneumonia and measles in children, or in contagious digestive diseases in children, such as infantile diarrhea and hand, foot, and mouth disease. [24-26]

Aim of the study;

This study was designed to;

1. Show the therapeutic effect of vitamin A on patients with COVID 19.
2. Show the protective effect of the vitamin A administration on contacts.

Subject and method

The study was done in the Anbar governorate west of Iraq from the beginning of June 2020 on diagnosed patients with COVID-19 and contacts with diagnosed patients. Informed consent was taken from families after giving them a full explanation about the purpose of the study. Two groups of samples were taken in this study;

1. The first group consists of 100 diagnosed patients with COVID-19. The selected cases were from mild to moderate groups, previously healthy, from deferent genders and the same residential area. 50 patients were given (200,000) international units of vitamin A on the first day and the same dose was repeated the next day. Another 50 patients were given a placebo. The vitamin and placebo were given to the patients as early as the diagnosis was established.

Exclusion criteria;

a. Patients with old ages >60 years.[27]

b. Patients with diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression, and cancer.[27]

c. Patients with severe disease (respiratory rate > 30 breaths/min, or SpO2 < 90% on room air).[1,27]

d. Pregnant women.[6]

A questionnaire data form was prepared for each patient before giving the vitamin A and after 24 and 48 hours from therapy about the clinical features and clinical findings according to WHO classification [1,26] including;

1.Cough.
2.Fever.
3.Fatigability.
4.Loss of smell and taste.
5.Headache.
6.Anorexia.
7. SpO2 .
8. The duration of illness. Recorded from the time of given vitamin A or placebo.
9.Number and percentage of patients who deteriorated to severe disease.

2. The second group, the study was done on contacts of patients with COVID-19 patients. Part of them given vitamin A (200,000 international unit) on the first day and repeated the next day, another part of contacts was given a placebo. The comparison was done on the incidence of getting COVID-19 from contacts, and the duration of the symptoms among those who got the infection.

Data collected were checked for accuracy and completeness and were coded and entered into the Statistical Package for Social Sciences (SPSS), Descriptive statistics for all studied variables and Chi-squared test were used and P-value level <0.05 was considered significant throughout the study.

RESULTS

Regarding the first group of 100 patients. There was a significant improvement of clinical features (fever, headache, anorexia, and fatigue) among the 50 patients who received vitamin A in comparison to the other 50 patients who received a placebo. Table 1. Mean SPO2 changes among patients given vitamin A after 24 and 48 hours had a slightly non-significant improvement than that reported among the placebo. Table 2. The mean duration of symptoms among patients given vitamin A was (2.9) while among those receiving placebo was (4.64). Table 3. Two patients (4%) from those given vitamin A deteriorate their SPO2 and need admission in isolation centers while 6 patients (12%) of those given placebo deteriorate their SPO2 and need admission in isolation centers. Table 4.

Regarding the second group, contacts to diagnosed COVID-19. From 97 contacts given vitamin A, only 20 (20.62%) of them got an infection with COVID-19. While from 112 contacts given placebo 65(58.03%) got the infection with COVID-19, with a significant difference. The duration of symptoms of infected contacts was (4.6) among those who received vitamin A comparing to (6.72) among those given placebo. Table 5.

DISCUSSION

Studies were limited or not done on the use of vitamin A in the treatment of COVID-19, but there were many other studies on the use of vitamin A in the treatment of deferent virus diseases especially in childhood viral infections like measles, chickenpox, and infantile diarrhea.[28]Even in some bacterial and protozoan infections.[29]

In the present study, we recommend the trial therapy with supplementation of vitamin A to patients diagnosed with COVID-19, and the results were compared with other patients with the same conditions not supplemented with vitamin A. Among the first group of mild to moderate patients, we found a significant improvement in clinical features, and duration of the symptoms of the disease, in addition to a lower number of patients who deteriorated to the severe stage among patients given vitamin A in comparison to control.

Regarding contacts with patients with COVID-19, in this study, we found that there was a lower significant difference in getting the infection in those who received vitamin A from those not received. And also, we found that symptoms among contacts who got the infections were shorter in those who received vitamin A from those not received.

The underlying mechanism of vitamin A in the treatment of COVID-19, may due to its anti-inflammatory property, or its effect on enhancing the humeral, cellular, or phagocytic immunity against the virus, or its repairing action on epithelial cells of the respiratory tract which needs further studies to explain this mechanism.

The limitations of the study included a small sample size, and excluding severe cases.

CONCLUSION

1. There was a significant improvement in signs and symptoms among patients with mild to moderate severity whose given vitamin A in comparison to control, with a shorter duration of symptoms.
2. A significantly lower number of patients who deteriorate to severe disease among patients given vitamin A.
3. A significantly lower incidence of infection among contacts received vitamin A with a shorter duration of the disease.

RECOMMENDATION

From the above results, the followings are recommended;
1.The addition of vitamin A in the treatment of COVID-19 protocol.
2.The use of vitamin A to all contacts and medical staff.
3. A big case-control study covering the whole country about the use of vitamin A in the management of COVID-19.

ACKNOWLEDGMENT

I would like to express my deepest gratitude and respect to the patients and their families, and all medical workers on the diagnosis of COVID-19 for their helpful advice, patience, and guidance throughout the execution of this study.

REFERENCES

1. World Health Organization.Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected";Geneva: on 13 March 2020.
2.Catharine Ross; Nelson's textbook of pediatrics; 21st ed. Philadelphia. 2020; chapter 61(Vitamin A deficiencies and excess) P;360-365.
3. Ross CA. Vitamin A. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:778-91.
4. WHO. Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency. Geneva, World Health Organization; 2009. (http://whqlibdoc.who.int/publications/2009/9789241598019_eng.pdf).
5. Olson JA. Vitamin A. In: Ziegler EE, Filer LJ, eds. Present knowledge in nutrition. Washington, DC: International Life Sciences Institute (ILSI) Press 1996:109–19.
6. Michael J. Dibley and David A. Jeacocke; Safety and toxicity of vitamin A supplements in pregnancy; Food and Nutrition Bulletin, vol. 22, no. 3 © 2001, The United Nations University.
7. Zhiyi Huang, Yu Liu; Role of Vitamin A in the Immune System; J. Clin. Med. 2018, 7, 258; DOI:10.3390/jcm7090258.
8. Mccullough F.S., Northropclewes C.A., Thurnham D.I. The effect of vitamin A on epithelial integrity. Proc. Nutr. Soc. 1999;58:289.
9. Ribery N., Tanumihardjo S.A. Oral doses of α-retinyl ester track chylomicron uptake and distribution of vitamin A in a male piglet model for newborn infants. J. Nutr. 2014;144:1188–1195.
10. Kiss I., Rühl R., Szegezdi E., Fritzsche B., Toth B., Pongrácz J., Perlmann T., Fésüs L., Szondy Z. Retinoid receptor-activating ligands are produced within the mouse thymus during postnatal development. Eur. J. Immunol. 2008;38:147–155.
11. Kuwata T., Wang I.M., Tamura T., Ponnamperuma R.M., Levine R., Holmes K.L., Morse H.C., De Luca L.M., Ozato K. Vitamin A deficiency in mice causes a systemic expansion of myeloid cells. Blood. 2000;95:3349.
12. Kang S.G., Park J., Cho J.Y., Ulrich B., Kim C.H. Complementary roles of retinoic acid and TGF-β1 in the coordinated expression of mucosal integrins by T cells. Mucosal. Immunol. 2011;4:66–82.
13. Ohoka Y., Yokota A., Takeuchi H., Maeda N., Iwata M. Retinoic acid-induced CCR9 expression requires transient TCR stimulation and cooperativity between NFATc2 and the retinoic acid receptor/retinoid X receptor complex. J. Immunol. 2011;186:733–744.
14. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of Vitamin A in the Immune System. J Clin Med. 2018 Sep 6;7(9):258.
15. Ghodratizadeh S., Kanbak G., Beyramzadeh M., Dikmen Z.G., Memarzadeh S., Habibian R. Effect of carotenoid β-cryptoxanthin on cellular and humoral immune response in a rabbit. Vet. Res. Commun. 2014;38:59–62.
16. Pantazi E., Marks E., Stolarczyk E., Lycke N., Noelle R.J., Elgueta R. Cutting Edge: Retinoic Acid Signaling in B Cells Is Essential for Oral Immunization and Microflora Composition. J. Immunol. 2015;195:1368–1371. DOI: 10.4049/jimmunol.1500989.
17. Heine G., Hollstein T., Treptow S., Radbruch A., Worm M. 9-cis retinoic acid modulates the type I allergic immune response. J. Allergy. Clin. Immunol. 2018;141:650–658.
18. Seo G.Y., Lee J.M., Jang Y.S., Kang S.G., Yoon S.I., Ko H.J., Lee G.S., Park S.R., Nagler C.R., Kim P.H. Mechanism underlying the suppressor activity of retinoic acid on IL4-induced IgE synthesis and its physiological implication. Cell Immunol. 2017;322:49–55.
19.Alabama O., Franke M.F., Huang C.C., Galea J.T., Calderon R., Zhang Z., Becerra M.C., Smith E.R., Ronnenberg A.G., Contreras C., et al. Impact of Vitamin A and Carotenoids on the Risk of Tuberculosis Progression. Clin. Infect. Dis. 2017;65:900–909.
20.Qrafli, M.; El Kari, K.; Aguenaou, H.; Bourkadi, J.E.; Sadki, K.; El Mzibri, M. Low plasma vitamin A concentration is associated with tuberculosis in Moroccan population: A preliminary case-control study.BMC Res. Notes 2017, 10, 421.
21.Wheelwright, M.; Kim, E.W.; Inkeles, M.S.; De Leon, A.; Pellegrini, M.; Krutzik, S.R.; Liu, P.T. All-trans retinoic acid triggered antimicrobial activity against Mycobacterium tuberculosis is dependent on NPC2.J. Immunol. 2014, 192, 2280–2290.
22. Makinde O., Rotimi K., Ikumawoyi V., Adeyemo T., Olayemi S. Effect of vitamin A and vitamin C supplementation on oxidative stress in HIV and HIV-TB co-infection at Lagos University Teaching Hospital (LUTH) Nigeria. Afr. Health Sci. 2017;17:308–314.
23.Wiysonge, C.S.; Ndze, V.N.; Kongnyuy, E.J.; Shey, M.S. Vitamin A supplements for reducing mother-to-child HIV transmission. Cochrane Database Syst. Rev. 2017, 9, CD003648.
24. Huang Z. Role of vitamin A in the immune system. J Clin Med. 2018;7(9):258.
25.Nan, H.U.; Qu-Bei, L.I.; Zou, S.Y. Effect of vitamin A as an adjuvant therapy for pneumonia in children: A meta-analysis. Chin. J. Contemp. Pediatr. 2018, 20, 146–153.
26.Chen, S.; Yang, Y.; Yan, X.; Chen, J.; Yu, H.; Wang, W. Influence of vitamin A status on the antiviral immunity of children with hand, foot, and mouth disease. Clin. Nutr. 2012, 31, 543–548.
27.IMAI District Clinician Manual. Hospital care for adolescents and adults. Geneva: World Health Organization; 2020. (https://apps.who.int/iris/bitstream/handle/10665/77751/9789241548290_Vol2_eng.pdf?sequence=3, accessed 13 May 2020).
28.Chen, S.; Yang, Y.; Yan, X.; Chen, J.; Yu, H.; Wang, W. Influence of vitamin A status on the antiviral immunity of children with hand, foot, and mouth disease. Clin. Nutr. 2012, 31, 543–548.
29.Semba RD. Vitamin A and immunity to viral, bacterial, and protozoan infections. Proc Nutr Soc. 1999;58(3):719-727. DOI:10.1017/s0029665199000944.

TABLES

Table.1. Number and percentage of patients among different symptoms before and after vitamin A and placebo administration.

Symptoms	Variables	No and % before	No and % after 24 hr	No and % after 48 hr	Significant
Fever	Vitamin A	35 (70%)	15 (30%)	10 (20%)	P=0.006
	Placebo	32 (64%)	25 (50%)	30 (60%)	
Anorexia	Vitamin A	32 (64%)	13 (26%)	11 (22%)	P=0.002
	Placebo	39 (78%)	23 (46%)	20 (40%)	
Headache	Vitamin A	42 (85%)	18 (36%)	12 (24%)	P<0.0001
	Placebo	44 (88%)	32 (64%)	37 (74%)	
Fatigability	Vitamin A	40 (80%)	22 (44%)	14 (28%)	P<0.0001
	Placebo	38 (76%)	41(82%)	40 (80%)	
Cough	Vitamin A	25 (50%)	25 (50%)	23 (46%)	P=0.345
	Placebo	30 (60%)	31 (62%)	31 (62%)	
Loss of smell and taste.	Vitamin A	23 (46%)	23 (46%)	20 (40%)	P=0.47
	Placebo	25 (50%)	30 (60%)	30 (60%)	

Table 2. SPO2 changes after 24 and 48 hours with vitamin A and placebo administration.

Variables	Mean before giving	Mean after 24 hr	Mean after 48 hr
Vitamin A administration	95.4%	97.17%	97.24%
Placebo administration	96.8%	94.42%	95.72%

P-value among mean SPO2 changes was =0.87

Table 3. Mean duration of symptoms among patients given vitamin A and placebo.

Variables	Mean duration of symptoms
Vitamin A administration	2.9
Placebo administration	4.64

Table 4. Number and percentage of patients who convert to the severe form.

Variable	Number of patients	Convert to severe disease	Percentage
Vitamin A administration	50	2	4%
Placebo administration	50	6	12%

P-value among deferent variables was <0.0001

Table 5. Incidence of getting infection and duration of symptoms among contacts in between that given vitamin A and placebo.

Variables	Number of contacts	Number and percentage of getting the infection	Mean duration of symptoms to infected patients
Vitamin A administration	97	20(20.62%)	4.6
Placebo administration	112	65(58.03%)	6.72

P-value among the incidence of the disease was <0.0001