ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 02, pp.25670-25677, February, 2019

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

ANALYSIS OF VITAMIN D EFFECTIVENESS OF SHORT INTERVENTIONS IN THE PREVENTION AND REDUCTION OF SEPSIS IN BRAZILIAN INTENSIVE CARE: A SYSTEMATIC REVIEW

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ARTICLE INFO

Article History:
Received 20th November, 2018
Received in revised form
06th December, 2018
Accepted 17th January, 2019
Published online 27th February, 2019

Key Words:
Vitamin D, Sepsis, Septicemia, Intensive therapy, Vitamin D deficiency, Vitamin D insufficiency, Septic shock.

ABSTRACT

Changing the percentage of vitamin D in the body causes severe organ dysfunction in intensive care patients. This study aimed to characterize the use of vitamin D in sepsis in Brazilian territory, reporting its beneficial effects in intensive care. The methodology used was the systematic review, using PRISMA method to select the studies used. As a result, they found that levels lower than the proposed standards, develop serious alterations in patients in intensive care. It is concluded that vitamin D supplementation by health professionals enabled in their practice results in the improvement of clinical conditions in relation to the organic dysfunction of the patient in intensive care.

Citation: Eliza Miranda Ramos, Valter Aragão do Nascimento, Matheus Dullius de Lima and Gilberto Gonçalves Facco, 2019. "Analysis of vitamin d effectiveness of short interventions in the prevention and reduction of sepsis in Brazilian intensive care: A systematic review", *International Journal of Development Research*, 9, (02), 25670-25677.

INTRODUCTION

When addressing the homeostasis of calcium metabolism the vitamin D is frequently recognized (Van *et al.,* 2003), even though it is called vitamin, at the same time it is a hormone classified as both steroid (Arson *et al.,* 2012), really, pleiotropic in the same way as pre-hormone and now as prohormone (Hamada *et al.,* 2007). It is mainly emphasized that vitamin D organizes the regulation of the metabolic process of calcium and phosphorus which is considered an important osteomineral physiological regulator (Hu *et al.,* 2013). However, the fully accommodative composition of vitamin D receptors in human cellsrecalls that it is compromised in systemic homeostasis (Jeng *et al.,* 2009). Thus, vitamin D deficiency has been a subject of great interest in the scientific community (Jeng *et al.,* 2009) and the search for information about its role in critical patients hospitalized in intensive care units is increasing (Drechsler *et al.,* 2010). Preliminary randomized studies have demonstrated the role of vitamin D as well as in the adaptive response to innate (Pecovnik-Balon *et al.,* 2009). The insufficiency of vitamin D leads to imbalance of the immune system (Ginde *et al.,* 2011) vitamin D probably has a preliminary role in defense against bacterial agents and viral by means of stimulation of antimicrobial peptides which intensifies the reduction of cathelicidins (Adorini e Penna, 2008) and the serum concentrations of vitamin D obtain a better advance in this case (Lee, 2011), in a sample of patients in intensive care with septicemia in reference to non-septic patients (Mckinney *et al.,* 2011). Also, the role of Immunomodulators should be inserted of the vitamin D identifies and annuls the effect of inflammatory cytokines especially interleukins 6 (IL-6) (Zipitis *et al.,* 2008) which induces the syndromes of systemic inflammatory responses (Jeng *et al.,* 2009). That is, by exploring the Immunomodulators role it can be complemented

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that is the result of an absence in the immunological regulation environment by Vitamin D (Quraishi *et al.,* 2015), previous experimental studies have aroused caution regarding the regulatory properties of vitamin D in this case, in different immune cells (Simpson e Brooks, 2008), encompassing the inhibition of the production of immunoglobulin G in the occurrence by plasma cells (Van *et al.,* 2003). The prevalence of vitamin D in patients admitted to the intensive care unit severe with or without sepsis shows a high rate of variation in the studies the according to the relative impact in a percentile of 38% to 100 % (Amrei *et al.,* 2011), approaching a higher relative frequency value in hospitalized patients in uncritical units (Berwick e Kesler, 2005). Thus, it is observed that a low serum vitamin D concentration during the admission process of the sepsis patient in intensive care is usually associated with a higher intensity of organic disease (Venkantram *et al.,* 2011).Studies have been published that the use of vitamin D supplementation has been shown to limit morbidity and to aggregate longevity in the general population that is lower levels of vitamin D (Alves *et al.,* 2015)referring to values such as such as 17.8 ng / mL have been related to the increased risk of death in 26%in relation to all admissible causes in the general population and patients with severe sepsis (Rech *et al.,* 2014), especially in septic shock still had vitamin D concentration with lower limit (Morimazato *et al.,* 2014) compared to septic patients without organic dysfunction (Prya *et al.,* 2015).Studies are reviewing and reorganizing knowledge regarding the vitamin D deficiency, which has shown a high prevalence in critically ill patients in intensive care (Santos *et al.,* 2007), however, vitamin D insufficiency seriously alters organ dysfunctions in patients in intensive care (Prya *et al.,* 2015).

In view of the high costs correlated with hospitalization in an intensive care unit (Drechsler *et al.,* 2010), with high and high values with a prevalence of increase in the hospital cost of 700% (Pecovnik-balon *et al.,* 2009), when compared to the costs of other hospitalizations in hospital clinical units (Alves *et al.,* 2015), related to vitamin D deficits (Holick, 2007). There are questions regarding the clinical factor not assimilated to the use of vitamin D in patients with sepsis (Arson *et al.,* 2012), for example, by increasing the dosage of vitamin D supplementation aggressively in populations with septic disorders in intensive care a change in disease outcome? If this change occurs in the disease outcome (Holick, 2007), then what is the ideal dose with beneficial effects to be used in intensive care for a positive approach to sepsis? There are questions regarding the clinical factor not assimilated to the use of vitamin D in patients with sepsis (Jeng *et al.,* 2009), for example, by increasing the dosage of vitamin D supplementation aggressively in populations with septic disorders in intensive care there may be a change in disease outcome (Lee, 2011)? If this change occurs in the outcome of the disease then what is the ideal dose with beneficial effects to be used in intensive care for a positive approach in sepsis (Mckinney *et al.,* 2011)? Due to the high percentile infiltration of sunlight in the Brazilian territory and its great territorial extension and with increased growth in the occurrence of sepsis in intensive care (Hu *et al.,* 2013), therefore, the objective of this systematic review was to characterize the use of vitamin D in sepsis in Brazilian territory in reporting its beneficial effects in intensive care (Ginde *et al.,* 2011).Regarding sepsis it is worth mentioning that it is a complex syndrome caused by the systemic inflammatory response rampant in the individual of infectious origin and characterized by multiple signs (Zipits e Akobeng, 2008) which may determine in this case the anomaly of one or more organs or even death (Ginde *et al.,* 2011). The use of the term septicemia, or sepsis (Jeng *et al.,* 2009) is not restricted only to secondary systemic inflammatory syndrome to bacterial infection but to that resulting from any microorganism (Desai *et al.,* 1998), that is, its products (toxins) (Venkatram *et al.,* 2011). Consequently, this review introduces important information about the occurrence of sepsis in intensive care patients (Berwick e Kesler, 2005) specifically in the Brazilian territory since the objective of this systematic review is to describe whether the use of vitamin D presents benefits in the clinical setting in the patient with sepsis in intensive care, only to serve as a clinical intervention for managers of intensive care units health professionals, patients and family members oriented by health professionals.

MATERIALS AND METHODS

A systematic review (RS) of studies on vitamin D use in patients with sepsis in intensive care was performed (Santos *et al.,* 2007). The bibliographic search was based on these four indispensable items in order to answer the questioning of the study, in the case, the PICO method (Santos *et al.,* 2007) was used which is described by the treaty in relation to the problem or the population (P), the intervention (I), comparison (C) and the (O) outcome. This method resulted in the delimitation of the following questions to which the study conducted: Is the use of vitamin D presents benefits in the clinic setting in patients with sepsis in intensive care? Each PICO treaty represented a part to be analyzed, being considered the inclusion criteria for analysis: Septicemia, patients with sepsis / septic shock (P), Vitamin D supplementation in intensive care (I), Dosage used of vitamin D in intensive care (C) and Clinic improvement of the patient with septicemia according to the respective dosages (O).

Identification of studies and research method

We analyzed indexed publications in the databases PubMed, Medline, Lilacs, Web of Science (Thomsons Reuters), the Scopus platform, and the COCHRANE library, previous editions of the second semester of 2018. The research was conducted by four independent reviewers (E.M.R, V.A.N, M.D.d.L, G.G.F), discriminating the free search strategy with health descriptors (Decs) in English and Portuguese: "septicemia", "vitamin D", "sepsis", "intensivism", "intensive therapy", "infection", "Septic shock", "deficiency", "sufficiency" and "insufficiency" the strategy used Boolean operators ("and" and "or" and "and not"), included studies published in the period from 2000 to 2018.The search for articles was conducted between April 31, 2018 and January 2019. In order to certify the quality of the systematic review, 31 the protocol Preferred Reporting Items for Systematics Reviews and Meta-analyses (PRISMA)in this study (De-la-Torre-Ugarte-Guanilo *et al.,* 2007). The articles were selected in the complete reading study evaluating the vitamin D delineation related to sepsis in intensive care, these studies were weighted, and subsequently selected according to the eligibility criteria to be included: randomized studies, preferably observational cohort or case study -control, which reports a population in intensive care with hypovitaminosis D explain which conditions were used for vitamin D, included relevant data to calculate the effect size, justified by the total

of 25 (OH) D and reported at least one of the following negative results: mortality, changes in the design of mechanical ventilation, long-term use of vasoactive agents in intensive care, changes in disease severity levels, population sampling equal to 25 or higher, absence of control group in the period the research. The aim of this study was to maintain mortality as a primary clinic profile. Only studies with patients older than 21 years of age, population greater than 25 patients, and vitamin D control (dosage) were performed during hospitalization in an intensive care unit. The quality of the articles selected was performed by two authors (E.M.R; M.D.d.L). The inclusion criterion for quality evaluation was in the initial process discussed between both and the evaluation was performed together. The divergences were discussed, and by consensus decisions were made. We used the instrument presented by Downs and Black, which consists of 27 questions regarding the quality of information of the articles, internal validity (You were confused), external validity, and statistical power, giving rise to a score ranging from zero to twenty-seven points. Any of the articles were classified according to quality and evidence and not the exclusion factor, because, evaluating the available evidence in relation to the topic and relating to the results found has a higher factor in the systematic review. The articles were classified in terms of quality of evidence, so the score was identified as follows (De la-Torre-Ugarte-Guanilo *et al.,* 2011): excellent (24 to 27), good (20 to 23), reasonable (15 to 19) and limited (14 or less), this classification pattern was adopted in other review studies. Were considered the studies that reached a score equal or superior to 21 points.

The research was performed independently by four researchers (E.M.R, V.A.N, M.D.d.L., G.G.F) and obtained complete articles from all citations that met the predefined selection criteria. The analysis of the articles was made from the titles, abstracts and full texts of the publications. It is worth noting that, in situations of divergence, they were resolved through one of the reviewers (G.G.F).The data were grouped in spreadsheets of the program Excel 2013. Absolute and relative frequencies were calculated and a calculation of the disruption of the use of vitamin D in relation to the interventions occurred was performed.

RESULTS

The searches totaled 361 articles, and after the exclusion by duplicates articles remained, according to the eligibility of articles. The articles excluded because they did not have used vitamin D dosage, improvement in the intensive care hospitalization according to the respective dosages totaled (n = 20). In the end, ten studies covered all inclusion criteria (Figure 1) and were included in the systematic review. When evaluating the quality of the selected articles, which was expressed in Table 1, the mean score was 21 points for articles included in the systematic review study according to the instrument using Down and Black (1998). In relation to the evaluation of the present items for evaluation in the instrument, in the case of Down and Black the dilemmas found were those related to the methodology, such as, external validity, internal validity and confounding (see selection) .

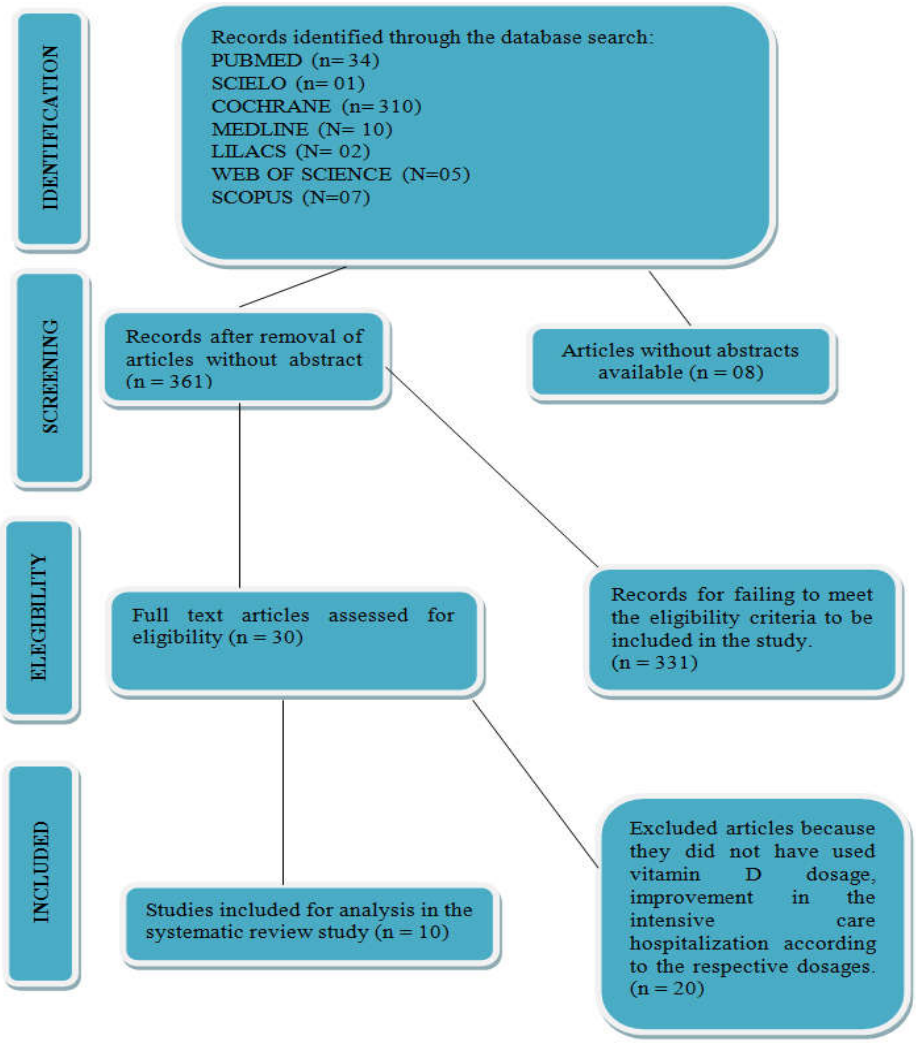

Figure 1. Flowchart of the selection process of the studies for inclusion in a systematic review

Table 1. Characterization of the articles selected for the systematic review study in agreement with the Down and Black criteria, Brazil. 2018

Author / year / alphabetical classification of article	Reporting (0 – 10)	External validity (0 – 03)	Internal validity – bias (0 – 07)	Confusion - bias of selection (0 – 06)	Power (01)	Total score
Venkatram; Chilimuri; Adrish, Salako; Madanmohan; Diaz-Fuentes. (2011) (A)	10	03	04	04	01	22
Alves; Freitas; Bafi; Azevedo; Machado. (2015) (B)	09	03	04	04	01	21
Priya; Venkatesh; Bala; Lee, Paul; FRACP; Kerr, Stephen; Hoechter, Dominik; Dimeski; Goce; Grice; Jeffrey; Myburgh, John; Jacqueline. 2015 (C)	08	02	06	06	01	23
Moromizato; Takuhiro; Litonjua; Augusto; Braun, Andrea; Gibbons; Fiona; Giovannucci; Christopher; Kenneth. 2014 (D)	09	03	07	06	01	26
Rech; PharmD; BCPS, Hunsaker; Rodriguez. 2014(E)	07	01	06	06	01	21
Quraishi; Sadeq; De Pascale; Gennaro; Needleman; Joseph;Nakazawa; Harumasa; Kaneki; Massao; Bajwa, Ednan; Camargo, Carlos; Bhan, Ishir. 2015 (F)	08	03	06	06	01	24
Zughaier; Jessica; Alvarez; Sloan; Konrad; Tangpricha. 2014. (G)	09	03	06	05	01	24
Leaf; Raed; Donnino; Ginde; Waikar. 2014(H)	08	03	06	06	01	24
Lasky-Sul; Dahlin; Litonjua; Rogers; McGeachie1; Baron; Gazourian; Barragan-Bradford; Fredenburgh; Choi; Mogensen; Quraishi; Christopher. 2017 (I)	09	03	06	06	01	25
Jeng; Yamshchikov; Judd; Blumberg; Martin; Ziegler; Tangpricha. 2009 (J)	08	03	06	06	01	24

SOURCE: SARA, H. D.; BLACK, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health.v.52. p.377–384. 1998.

Table 2. Comparison of the diagnosis of sepsis according to sex and vitamin D deficiency in the analyzed studies, Brazil. 2018

Study	Sex M	%	Sex F	%	Sepsis				Vitamin d deficiency	%
					Yes	%	Not	%		
A	208	47,5	229	52,5	157	35,9	280	64,1	340	77,8
B	30	58,8	21	41,2	26	51,0	25	49,0	35	68,6
C	36	72,0	14	28,0	10	20,0	40	80,0	28	56,0
D	1489	44,0	1897	56,0	240	7,08	3146	92,0	240	7,08
E	30	31,5	65	68,4	69	72,6	26	27,4	65	68,4
F	52	60,0	35	40,0	36	41,3	51	58,7	43	49,4
G	115	48,8	121	51,2	206	87,2	30	12,8	24	10,2
H	60	66,6	30	33,4	31	34,4	59	65,6	72	80,2
I	95	42,0	130	58,0	135	60,0	90	40,0	91	41,0
J	45	64,2	25	35,8	45	64,2	25	35,8	47	66,5

DISCUSSION

Our results showed that 6 articles (60%) performed a diagnosis of sepsis during the study period which confirmed the presence of sepsis / septicemia / septic shock in studies included in the systematic review at admission or 48 hours after admission this result was statistically significant for those with vitamin D deficiency (Venkatram *et al.,* 2011), this systematic review continued with a frequency above 50% in vitamin D deficiency that is the result of the studies analyzed suggests a relationship between the probability of infection and the vitamin D deficiency (Alves *et al.,* 2015). The study of this review pointed out that the estimation of the significance of the effect of the use of vitamin D (Prya *et al.,* 2015) in patients with sepsis obtained a concordance with serum concentration deficit (Rech *et al.,* 2014). We highlight previous studies which indicated that vitamin D receptors are available in almost all human cells and tissues including the heart (Leaf *et al.,* 2014), brain, colon and system cells (Zughaier *et al.,* 2014), therefore its relevance in the maintenance of the immune system (Jeng *et al.,* 2009). Studies A, B, E, F, H and J reinforce in relation to severe sepsis infection in presenting a high prevalence of vitamin D deficiency (Rech *et al.,* 2014), which are followed by a high rate of death (Moromizato *et al.,* 2014). Study D and F implied that vitamin D deficiency should be considered a risk factor for sepsis in relation to the researched epidemiological population (Alves *et al.,* 2015) since studies suggest that vitamin D is important in immunomodulation through the regulation of inflammation in this case (Morimazato *et al.,* 2014), cytokines (Rech *et al.,* 2014), cell proliferation, cell differentiation and apoptosis (Quraishi *et al.,* 2015), and may even act in the homeostasis of calcium, magnesium, phosphate and of the classic bone formulation (Zughaier *et al.,* 2014).

This systematic review on differentiation in relation to vitamin D (Morimazato *et al.,* 2014) is a hormone that influences more than genes in the human body (Jeng *et al.,* 2009) which can play a crucial role in the maintenance of health (Lasky-Sul *et al.,* 2017). The reviewed studies found a combination between vitamin D deficiency and the sepsis syndrome (Prya *et al.,* 2015). Moreover, the result reinforces that the problematization of sepsis in critically ill patients with vitamin D (Alves *et al.,* 2015) deficiency occurs according to changes in metabolism of glucose and especially of calcium or disorder of the immune cells and endothelial cells occurred according to the deficiency (Venkatram *et al.,* 2011). However, the strengths of this systematic review are related to serum vitamin D (Venkatram *et al.,* 2011) which proposes a relationship between the infection rate and vitamin D deficiency a trend that is reinforced by the increase in nosocomial infection in intensive care for those with hypovitaminosis (Quraishi *et al.,* 2015).The studies analyzed indicate that hypovitaminosis D (Moramizato *et al.,* 2014) is related to the longer time of hospitalization and a greater increase in the probability of contracting infections in intensive therapy (Leaf *et al.,* 2014). However, it is known that the positive effect in relation to the normal level of vitamin D is essential for optimal health during hospitalization (Jeng *et al.,* 2009). It should be remembered that the current intensive care centers do not routinely evaluate the vitamin D concentration sequence (Lasky-Sul *et al.,* 2017) and low levels of vitamin D (Jeng *et al.,* 2009) are common in the adult population in general and as a consequence have been associated with serious infectious diseases such as sepsis during intensive care hospitalization (Rech *et al.,* 2014).This systematic review study confirms according to previous experimental studies that the high prevalence of low levels of vitamin D in severe patients triggers changes in the immune system which may have as a consequence sepsis (Quraishi *et*

al., 2015). The metabolism of vitamin D or 25-hydroxyvitamin D or 25 (OH)D (Leaf *et al.,* 2014) occurs in the liver which is presented as an active half-life inactive precursor 1,25 (OH)D (Rech *et al.,* 2014)with a time-delay response of only to 24 hour (Zughaier *et al.,* 2014). Therefore, a study indicates the importance of laboratory blood determination in the initial period of hospitalization for vitamin D (Venkatram *et al.,* 2011)since there is an easy determination of blood levels in the initial period of hospitalization (Rech *et al.,* 2014). Because of this ease of control of 25 (OH)D shows this nutritional aspect it can elaborate protocols that will reduce the risk of infection in intensive therapy with vitamin D blood control (Zughaier *et al.,* 2014).This systematic review reinforces the negative effect of the high prevalence of vitamin D insufficiency and deficiency (Venkatram *et al.,* 2011) in a sample of severely ill adults in intensive care units (Prya *et al.,* 2015).The quality of the evidence from the studies analyzed in this systematic review showed that vitamin D deficiency presents a high prevalence in critical patients and worsens the organic dysfunctions of these patients (Jeng *et al.,* 2009). One of the devices indicated for this high occurrence is the more frequent reduction of serum levels of the vitamin D transporters in patients such as sepsis (Rech *et al.,* 2014).This happens because of the time criteria of intensive care hospitalization which leaves the patients more favorable to present vitamin D deficiency in the case, represented in study A, F and G resulting in levels of vitamin D as insufficient ((Quraishi *et al.,* 2015).

In this systematic review hypovitaminosis D obtained the prevalence of being associated with adult and male patients (Morimazato *et al.,* 2014), however, some published studies have revealed a higher prevalence of vitamin D deficiency in women and patients over 60 years of age a result that was confirmed by study B, G and I (Jeng *et al.,* 2009), that is, there is no differentiation in relation to vitamin D deficiency when compared to sex (Morimazato *et al.,* 2014). In regard to the mechanism by which vitamin D deficiency causes so many health impacts to the patient in intensive care (Rech *et al.,* 2014), the studies I and F are concerned with macrophages (Lasky-Sul *et al.,* 2017), lymphocytes and monocytes ((Zughaier *et al.,* 2014), which have presented vitamin D receptor, when it is excited, with increased gene expression of an endogenous antimicrobial peptide and defensins (Rech *et al.,* 2014), known as catelicidin (Zughaier *et al.,* 2014). A positive percentage relationship between plasma levels of catecholines and serum levels of vitamin D in acute care patients with acute illnesses (Jeng *et al.,* 2009) such as sepsis (Lasky-Sul *et al.,* 2017), is considered, since this peptide is effective against bacteria (Jeng *et al.,* 2009), fungi and several entry sites of pathogens only through the mucosa of the respiratory system, as well as the digestive system and the skin (Alves *et al.,* 2015). Several devices have been proposed to explain the importance and participation of vitamin D (Alves *et al.,* 2015) in the physiology and alterations that triggers the diseases of the immune system specifically (Jeng *et al.,* 2009) the presenting cells of antigens (CAA) in this case monocytes (Venkatram *et al.,* 2011), macrophages and dendritic cells, for example, when inhibiting the release of p7015 (Zhugaier *et al.,* 2014) we observe the inhibition of cytokines pro-inflammatory agent IL-11 (Leaf *et al.,* 2014) and TNF by monocyte cells and macrophages (Rech *et al.,* 2014).Study G confirms in its experimental research that macrophages (Venkatram *et al.,* 2011) play a central role in iron metabolism and host defense, so they are also excellent producers of inflammatory cytokines and treatment with Vitamin D (Alves *et al.,* 2015).The mechanism used for Vitamin D to exert the anti-inflammatory effects is recently proposed to be mediated by microRNA which receives the name of miR-155 (Rech *et al.,* 2014). In addition to miR-155 and the vitamin D can regulate the immune system by inducing autophagy and regulating endoplasmic stress thus playing an essential role in cellular homeostasis and host defense (Morimazato *et al.,* 2014). Normally, the values have been validated with median vitamin D standards with a variance between 4 to 20 ng / dLbeing compatible with the standard established in this study (Alves *et al.,* 2015), whose vitamin D interval was according to the range of 0 to 20 ng / dL for inclusion in the studies (Quraishi *et al.,* 2015).

Associated with this vitamin D interval patients with vitamin D levels below 20 ng / dLbecome disqualified from fully developing catatelicidin (Zhugaier *et al.,* 2014) because this may be related to increased susceptibility to nosocomial infection such as pneumonia (Leaf *et al.,* 2014), sepsis among other adversities in the renal system, cardiac and neurological (Rech *et al.,* 2014). In its contribution, study B, C and G, from the systematic review, suggests that vitamin D deficiency may increase metabolic disorders related to immunodeficient regulation which may lead to worse results than would be practical use in individuals with normal levels of vitamin D because vitamin D has a binding protein which is not only the carrier of the only two forms of vitamin D (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) (Prya *et al.,* 2015), however, has the physiological role of sequestering monomeric actin thus hindering its polymerization in F-actin. The individuality of the actin binding of DBP (vitamin D binding protein) (Alves *et al.,* 2015) may play a protective role in sepsis and avoid the polymerization of actin released into the tissue lesion which may result in the microembolization of the terminal organs (Lasky-Sul *et al.,* 2017) aggregation of actin with vitamin D binding protein (DBP) results in decreased concentrations of this binding protein because it reduces a percentile greater than 25 (OH)D (Jeng *et al.,* 2009) as a consequence of renal loss of vitamin D and its metabolites (Prya *et al.,* 2015), this mechanism provides us with an understanding of the existence of insufficiency of vitamin D in sepsis (Alves *et al.,* 2015).

Finally, it seems plausible that patients with deficient serum vitamin D levels and insufficient are less able to mount a sufficient response to infection (Alves *et al.,* 2015).It should be emphasized that immunosuppression may be a consequence of surgical and invasive procedures which are common situations in an intensive care unit and have been shown to prescribe nosocomial infections (Prya *et al.,* 2015). It is important to emphasize that the causes of vitamin D deficiencies are multifactorial (Venkatram *et al.,* 2011) such as: age over 60 years, low index of exposure to sunlight, decrease in dietary intake of vitamin D, comorbidity and possible interactions with drugs used in intensive care (Rech *et al.,* 2014).However, critically ill patients often exhibit progressive risk of vitamin D deficiency (Quraishi *et al.,* 2014), low exposure to sunlight and decreased levels of dietary supplementation (Zughaier *et al.,* 2014).As a consequence, it is recognized that the high cost related to hospitalization in intensive care centers shows high values (> 700%) at the time that is verified to the costs of the other hospitalizations (Venkatram *et al.,* 2011). The results of this systematic review, together with serum levels below 20 ng / mL (Alves *et al.,* 2015), showed a high impact of intensive care patients (Prya *et al.,* 2015), mainly associated with

Table 3. Result of the effect of Vitamin D supplementation on mortality in intensive care patients with sepsis diagnosis of blood Vitamin D oflow level (20 ng / mL), Brazil 2018.

Study	WITH USE OF SUPPLEMENTATION 25(OH)D				NO USE SUPPLEMENTATION 25(OH)D			
	With mortality	%	No mortality	%	With mortality	%	No mortality	%
A	29	18,4	63	40,2	56	35,7	09	5,70
B	07	26,9	05	19,2	10	38,6	04	15,3
C	06	60,0	01	10,0	02	20,0	01	10,0
D	85	35,4	125	51,2	20	8,34	10	4,16
E	25	36,2	29	42,2	10	14,4	05	7,24
F	10	27,7	16	44,4	06	16,6	04	11,2
G	74	35,9	86	41,7	36	17,4	10	4,85
H	20	64,5	01	3,22	07	22,6	03	9,68
I	35	25,9	65	48,4	26	19,0	09	6,66
J	05	11,1	20	44,4	12	26,2	10	19,0

mortality in the case of patients without vitamin supplementation D in the period of intensive care hospitalization (Moromizato *et al.,* 2014), for example, study A presented 35.7% of mortality without Vitamin D supplementation and was statistically reinforced by study Hwith a value of 64.5% (Venkatram *et al.,* 2011). Recently vitamin D insufficiency has been used for mortality in adult patients and in severe conditions (Leaf *et al.,* 2014). In this case, vitamin D supplementation was evidenced in the studies analyzed in this systematic review the credibility of decreasing mortality and increasing immune resistance in the intensive care population (Rech *et al.,* 2014). Serum vitamin D levels inferred at 17.8 ng / dL have been reported to increase the risk of death by 26% from all justifications in the population in intensive care (Zughaier *et al.,* 2014).

In evaluating the impact of vitamin D deficiency the studies included that the length of stay in intensive care leaves patients more susceptible to mortality due to vitamin d deficiency (Prya *et al.,* 2015). The analyzed articles found a combination in relation to mortality and the high prevalence of hypovitaminosis D deficiency / insufficiency of vitamin D may increase mortality in critically ill patients (Jeng *et al.,* 2009), however, it is possible that hypovitaminosis D at the beginning of treatment acute disease is contributing to the negative end-points and benefit the increase in the length of stay in the intensive care unit (Venkatram *et al.,* 2009). Study B and H emphasized that patients who survived long-term intensive care hospitalization had significantly higher serum vitamin D (Alves *et al.,* 2015) levels when compared to those with mortality. In patients who supplemented vitamin D before the period of hospitalization in an intensive care unit with no intention of verifying possible finalizations (Venkatram *et al.,* 2011), mortality was significantly lower when compared to those who did not receive previous supplementation of this substance (Prya *et al.,* 2015). Article A, B, C and F, and reinforced by the final considerations in article B, since they reported that supplementation in the case (Prya *et al.,* 2015), the literature qualified the amount of vitamin D to be supplemented with the best results (Alves *et al.,* 2015), in order to obtain a significant increase in the serum levels of these nutrients, that is, it was clarified that the supplementation of 1500 to 5000 IU / day of 25 (OH)D (Alves *et al.,* 2015; Prya *et al.,* 2015) was the most efficient whose blood values normalized in 7 days (Jeng *et al.,* 2009). In view of this, it is important to emphasize again that the serum levels and the vitamin D supplementation in intensive care are not used as a reality in intensive care in Brazil (Lasky-Sul *et al.,* 2017).One of the negative points of this review is the existence of a disagreement in the doses and in the time of supplementation used (Jeng *et al.,* 2009).

The researches were done in different populations which may have contributed to the setbacks of the identified results (Venkatram *et al.,* 2011). Some studies of this systematic review emphasize that patients in therapy units with vitamin D deficiency are more susceptible to sepsis (Jeng *et al.,* 2009), whose alteration may still be an important cause of death in this population (Lasky-Sul *et al.,* 2017). Therefore, the studies consider that the high level of vitamin D in patients in intensive care avoids or accelerates the disorders of serious diseases such as sepsis. In relation to vitamin D supplementation in cases of deficiency or insufficiency of vitamin D, they are generally administered at doses of 1500 to 5000 IU / day (Alves *et al.,* 2015)and this dosage has been recommended by the Endocrine Society (Prya *et al.,* 2015), which appears to be well tolerated, with relatively minor concern about toxicity for most patients. In the context of intensive care, low levels of vitamin D and complications with negative results have been cited in previous studies (Alves *et al.,* 2015). This systematic review carried out an analytical and descriptive analysis to which it was associated that lower levels to standardized vitamin D are associated with greater intensity of organic dysfunction in this case complications such as sepsis (Rech *et al.,* 2014). Serial evaluation of the vitamin D concentration in the period of hospitalization was medically explored in the analyzed studies whose hospitalization periods ranged from 7 to 10 days (Moromizato *et al.,* 2014) determining the persistence of insufficient levels in the concentration of vitamin D high levels of vitamin D resulted in a decrease in hospitalization time and aggravation of organ dysfunction (Rech *et al.,* 2014). However, depending on the characteristics of the study, there is no possibility of classifying the cause and effect relationship because it is feasible to perform a comparison between the improvements of the clinical status of the patients analyzed through the laboratory score and the improvement in the serum concentration of vitamin D (Quraishi *et al.,* 2015). Vitamin D was associated with death in pulmonary dysfunctions because in addition to the data observed in seven studies (Rech *et al.,* 2014); however, this systematic review suggests that there is a possibility of vitamin D deficiency to amplify metabolic disorders heart disease and pulmonary diseases and especially alteration in the immune system which shows sepsis as an outcome (Rech *et al.,* 2014). It is worth emphasizing that vitamin D behaves like a metaphoric hormone capable of contributing to the good functioning of the cardiac muscle and of the respiratory system (Quraishi *et al.,* 2015). Of note in this study, the positive point in the studies was the use of control groups combined by indicators closed in the severity of the organic dysfunction which favored the construction of a more homogeneous sample in relation to other studies (Moromizato *et al.,* 2014).

Conclusion

The prevalence of vitamin D deficiency is high in patients diagnosed with sepsis. Vitamin D supplementation should be given in intensive care patients to achieve a normal serum concentration (Normality: 25 (OH) D ≥ 30ng / dL, according to the endocrinology society). In summary, the study demonstrates a direct association with the improvement of the clinical picture in comparison to the improvement of vitamin D deficiency, which shows a greater reduction in the indicators of the intensity of organic dysfunction, that is, vitamin D is increasingly recognized as an important agent of immune function and may be a preventive factor in the development of sepsis in patients in intensive care. It can be concluded that interventions with vitamin D supplementation by health professionals enabled in their practice result in improved clinical conditions in relation to the organic dysfunction of the patient in intensive care. The result of this systematic review provides important precedents for investing in clinical trials with large-scale intervention in adjuvant vitamin D therapy in several scenarios of organic dysfunction, including additional studies in the management of human sepsis and other critical illnesses.

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