Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Programa de Pós-graduação em Ciências Médicas: Endocrinologia

Tese de Doutorado

Avaliação de Alterações Hormonais em Pacientes Críticos

Aluno: Rafael Barberena Moraes
Orientador: Prof. Mauro Antônio Czepielewski

Porto Alegre, junho de 2013

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LISTA DE ABREVIATURAS

1,25[OH]2D	*1,25-dihydroxyvitamin D, calcitriol*
25[OH]D3	*25-hydroxyvitamin D3, vitamin D*
AIDS	*Acquired Immunodeficiency Syndrome*
APACHE II	*Acute Physiology and Chronic Health Evaluation II score*
BMI	*Body mass index*
CIA	*Cumulative Incidence Analysis*
CIRCI	*Critical Ilness-Related Corticosteroid Dysfunction*
CI	*Confidence Interval*
Δ	*Variation*
GH	*Growth Hormone*
IAR	Insuficiência Adrenal Relativa
ICU	*Intensive Care Unit*
IGF	*Insulin-like Growth Factor*
KM	*Kaplan-Meier*
LC-MS	*liquid chromatography-tandem mass spectroscopy*
PTH	*Parathyroid Hormone*
ROC	*Receiver-Operating Characteristic*
SIRS	*Systemic Inflammatory Response Syndrome*
SOFA score	*Sequential Organ Failure Assessment Score*
UTI	Unidade de Terapia Intensiva
VDBP	*vitamin D binding protein*

SUMÁRIO

INTRODUÇÃO

A criação de Unidades de Terapia Intensiva (UTIs) é um advento relativamente recente. Perante situações ameaçadoras de vida demandando internações por vezes prolongadas em UTIs, passamos a observar alterações na hemostasia até então desconhecidas. Neste cenário a avaliação do sistema endocrinológico representa um grande desafio.

Diversos fatores presentes na doença crítica fazem com que métodos diagnósticos empregados no paciente ambulatorial não sejam reprodutíveis no ambiente de UTI, seja pelas alterações causadas pela doença crítica, seja pelo viés induzido pela grande quantidade de cointervenções as quais o paciente crítico está exposto, tais como uso de vasopressores, analgésicos, sedativos, ventilação mecânica e outros. Como se comporta o sistema endocrinológico perante estas intervenções é tema cada vez mais presente na literatura. Nos últimos anos algumas das mais relevantes publicações na área de medicina intensiva são oriundas do estudo da endocrinologia do paciente crítico. Da mesma forma, cada vez mais a literatura endocrinológica tem dado espaço ao estudo das variações hormonais do paciente crítico. O conhecimento de temas como disfunção adrenal no paciente crítico, controle glicêmico, síndrome de T3 baixo, o sistema GH/IGFs na doença crítica, o paciente obeso na UTI, disfunções pituitárias após traumatismos cranienceфálicos, manejo pós-operatório de cirurgias adrenais e de tireóide ou o manejo do potencial doador de órgãos é indispensável para o cuidado do paciente crítico. Grande parte do desafio do estudo da endocrinologia do paciente crítico se deve a dificuldade de identificar quais alterações decorrentes do processo de patologia crítica são adaptativas e quais são patológicas, quais alterações apresentam relações causais com o desfecho do paciente e quais são meramente epifenômenos. Sendo a heterogeneidade a regra entre pacientes críticos, como definir critérios diagnósticos nesta população? Elucidar estas questões é um desafio extremamente instigante aos pesquisadores da área. Estas respostas são indispensáveis para que possamos identificar quais alterações hormonais decorrentes da patologia crítica devem sofrer intervenção terapêutica e quais devem apenas ser observadas.

No primeiro estudo desta tese abordamos uma questão extremamente discutida na literatura: o uso de esteróides em portadores de choque séptico. Os consensos atuais indicam o uso de hidrocortisona em portadores de choque séptico que não atingem estabilidade hemodinâmica após adequada ressuscitação hídrica e terapia vasopressora (1). A diferença observada nos principais ensaios clínicos sobre este tema se reflete em resultados divergentes

nas metanálises de revisões sistemáticas (2-7). Estas metanálises divergem quanto ao impacto de esteróides sobre mortalidade no choque séptico, embora concordem que esteróides apresentam efeito hemodinâmico benéfico, diminuindo tempo de uso de vasopressores. Abordamos um ponto até então pouco explorado nesta discussão. Conforme expusemos previamente (8) o teste de Kaplan-Meier superestima o efeito da intervenção em cenários onde há ocorrência de desfechos competidores, ou seja, quando a ocorrência de um desfecho impede a ocorrência de outro. É o que ocorre quando tentamos analisar a retirada de vasopressores, mas ocorre o desfecho competidor óbito. Embora o teste de Kaplan-Meier, seja amplamente difundido e executável na maioria dos programas estatísticos, entre as suas limitações encontra-se justamente a incapacidade de lidar com desfechos competidores, os quais são extremamente comuns no cenário de medicina intensiva (9, 10). Para lidar com esta situação diversos autores preconizam que perante desfechos competidores seja empregado o teste de Análise de Incidência Cumulativa. Esta técnica foi desenvolvida para lidar com o viés introduzido pela ocorrência de desfechos competidores, mas infelizmente ainda não é amplamente difundida nem executável na maioria dos programas estatísticos. (11, 12). Neste estudo aplicamos esta técnica a uma coorte de pacientes com choque séptico aferindo quanto o teste de Kaplan-Meier magnifica o efeito hemodinâmico dos esteróides. A partir destes resultados concluímos que a Análise de Incidência Cumulativa deveria ser mais amplamente empregada nos estudos que avaliam desfechos tempo-dependentes, podendo alterar a percepção do efeito dos esteróides sobre retirada de drogas vasoativas em portadores de choque séptico.

No segundo estudo que compõe esta tese abordamos um tema relativamente recente em medicina intensiva: o papel da vitamina D em pacientes críticos. A descoberta dos efeitos pleiotrópicos da vitamina D tem gerado crescente interesse a cerca da influência da vitamina D no cenário de medicina intensiva. Além dos efeitos hormonais da vitamina D no metabolismo ósseo, recentemente a literatura tem demonstrado que a vitamina D influencia atividade dos sistemas imunológico, cardíaco, vascular e respiratório (13). Alguns estudos têm relatado associação entre deficiência de vitamina D, morbidade e mortalidade em pacientes críticos (14). Apesar disto, diversas questões tangentes a relação entre o metabolismo da vitamina D e o curso do paciente crítico ainda não encontraram resposta. Os estudos observacionais, realizados na Europa, Austrália e América do Norte, até o momento não respondem se a vitamina D é meramente um marcador de gravidade ou se apresenta relação causal com morbimortalidade em pacientes críticos. Abaixo de que níveis há comprometimento dos efeitos pleitrópicos da vitamina D e consequente impacto no desfecho

do paciente crítico? Qual a importância da cinética da vitamina D durante a internação em unidade de terapia intensiva? As concentrações de vitamina D podem identificar pacientes com maior gravidade e desta forma serem usadas como monitorização de pacientes? E por fim, a reposição de vitamina D pode impactar a mortalidade em pacientes críticos? Tendo por base este racional teórico, apresentamos nesta tese de doutorado dois dos trabalhos desenvolvidos visando colaborar na elucidação do papel do sistema endocrinológico sobre o desfecho de pacientes portadores de patologia crítica.

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OBJETIVO

Com estes estudos objetivamos:

1. Analisar a influência de aspectos metodológicos e estatísticos sobre a influência de corticoterapia em portadores de choque séptico.
2. Avaliar em nosso meio a relação entre deficiência de vitamina D à internação em UTI, a cinética da vitamina D durante internação em UTI e morbimortalidade.

ARTIGO 1

Comparison of Cumulative Incidence Analysis and Kaplan-Meier for analysis of shock reversal in patients with septic shock

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Keywords: Cumulative incidence analysis; Kaplan-Meier; Septic shock; Time-to-event analysis; CIRCI (critical illness-related corticosteroid insufficiency)

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Abstract

Introduction: Kaplan-Meier (KM) has become the most used method to evaluate time-to-event analysis, although it is unsuitable in competing event situations such as death and shock reversal. Despite that the use of this methodology is not widely disseminated, cumulative incidence analysis (CIA) is more appropriate in these situations. We used CIA and KM (with 2 different techniques of censoring) to compare shock reversal in a cohort of patients with septic shock after steroid therapy. Furthermore, we have analyzed shock reversal in responders and nonresponders to high-dose cortrosyn test (250 μg).

Methods: Analysis of shock reversal in a cohort of 74 patients with septic shock at a university hospital was done.

Results: Shock reversal by the 28th day was estimated to be 88% and 72% by KM methods and 59% by CIA. In nonresponders to cortrosyn test ($\Delta \leq 9$ μg/dL), shock reversal was estimated in 80% and 56% according to KM and 47% according to CIA. As for responders to cortrosyn test, shock reversal was estimated in 90% and 77% according to KM and 64% according to the CIA method.

Conclusion: Kaplan-Meier overestimates shock reversal. Cumulative incidence analysis seems to be a more appropriate method to analyze shock reversal. Future trials intended to analyze shock reversal should apply CIA.

1. Introduction

In some medical situations, the main outcome is the time to an event, such as shock reversal in patients with septic shock. There are many methods to evaluate time-to-event data. Instead of "time-to-event," the word "survival" is commonly used to designate these methods, although the words are not synonymous. In common, these techniques estimate the probability of occurrence of events at every follow-up period for the population cohort [1,2].

Also known as "product-limit method," Kaplan-Meier (KM) has become the most conventional method to assess time-to-event analysis; besides, it is executable in most statistical software packages. In the scope of critical care, some trials have applied this methodology for the purpose of assessing the influence of steroid therapy in patients with sepsis and septic shock on shock reversal [3-6]. These trials and their respective meta-analysis allowed concluding that steroids decrease vasopressor dependence [7,8].

Shock reversal is currently the only consensual clinical benefit of steroids in patients with septic shock, mainly in patients with critical illness–related corticosteroid insufficiency that can be diagnosed as baseline serum cortisol concentration less than 10 μg/d or cortisol variation (Δ) 9μg/dL or less [9]. Although it has been ideally suited to analyze several time-to-event situations, KM is inadequate to analyze vasopressor withdrawal because it works with time set to a single type of event; thus, assuming independence between event and censoring. This assumption is not confirmed when analyzing shock reversal, as this is a competing event. Kaplan-Meier method is a "2-state model" [10]; in this example, at the beginning of the observation, all patients were in shock, whereas during follow-up, the curve showed a step-down as the patient exhibited shock reversal as an outcome. The problem is that some patients will exhibit the competing event "death" but before the main outcome (shock reversal) is disclosed during the follow-up period. Yet, there are different ways to deal with this limitation in KM techniques. The 2 most common ways are (1) at the moment the patient dies, he or she is censored, and; (2) the patients who die in shock during the follow-up are considered to have been in shock (alive) until the end of the follow-up period. These corrections induce bias in the interpretation of curves and may overestimate the incidence of shock reversal.

In scenarios where there are competing events, methodologies that correct the probability of 1 event to the competing event are more accurate and should be used. These methods bring into question the assumption the probability of another outcome (death), thereby correcting

the probability of the main outcome regarding the competing event. One of the terms used in the literature to designate such methodologies is “cumulative incidence analysis” (CIA). Unfortunately, researchers have only recently become aware of the benefits of this methodology [11].

In this study, both CIA and KM methodologies have been applied to compare estimates of shock reversal in a cohort of patients with septic shock after steroid therapy. We have also analyzed estimates of shock reversal based on the responses to cortrosyn test.

2. Materials and methods

Our study used data from a trial designed to compare low and high-dose cortrosyn tests (to be published). The trial included 74 patients older than 18 years sequentially submitted to both tests at a medical-surgical intensive care unit (ICU) of a tertiary university hospital; patients were prospectively enrolled from November 2006 to February 2009. Patients who were eligible for enrollment into the study were those who met the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Conference Consensus Committee [12] for septic shock; have systolic blood pressure less than 90 mm Hg, despite of adequate fluid replacement and use of vasopressor for at least 1 hour for a period inferior to 96 hours at the ICU; and were under invasive mechanical ventilation. The decision concerning low-dose hydrocortisone therapy after the cortrosyn test and other therapeutic decisions was taken at the discretion of the patient's physician without influence of researchers. The following were considered as exclusion criteria: previous use (short or long term) of cortisol; use of drugs known to suppress adrenal function, such as etomidate, spironolactone, oral contraceptives, or antifungals; AIDS; history of previous adrenal failure; pathology of hypothalamic-pituitary-adrenal axis; pregnancy; and shock due to other etiologies. All patients were submitted to high-dose (250 μg) cortrosyn test (tetracosactide, Synacthene; NOVARTIS, France). Serum cortisol concentration was measured at baseline 30 and 60 minutes after cortrosyn infusion. Cortisol variation (Δ) was calculated as the difference between peak serum cortisol concentration (30 or 60 minutes) and the baseline cortisol concentration before the cortrosyn test. Patients were considered nonresponders to the high-dose test when Δ cortisol is 9 μg/dL or less. Because of the overlap of results between responders and nonresponders to the low and high-dose cortrosyn tests, the analysis of the low-dose test was suppressed in this study. Serum cortisol analysis was performed by chemiluminescence (Modular E-170; Roche). The protocol was approved by the ethics

committee. The following variables were recorded: age, sex, admission category (medical or surgical), source of infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score [13], serum albumin, and glycemia. Patients were followed up for 28 days. Shock reversal was defined as systolic blood pressure more than 90 mmHg without vasopressor support for at least 24 hours.

3. Statistical analysis

Statistical analyses were conducted using SPSS 17.0 statistical package software (SPSS Incorporation, Chicago, Ill). The results of continuous variables are expressed as the mean ± SD. Shock reversal was estimated by KM and CIA methods. Cumulative incidence analysis was conducted as described by Ludbrook and Royse [14], and groups were compared by Cox proportional hazards to competing events [15]. Kaplan-Meier method allows different censoring applications. Two different approaches to KM have been performed. In the first approach (KM1), the occurrence of death before shock reversal resulted in censoring in the moment of death. In the second approach (KM2), the competing event death was ignored, that is, they were considered to be in shock until the end of the follow-up period. Mortality was estimated by the KM method, and results were compared between groups using the log-rank test. Furthermore, $P < .05$ was considered statistically significant.

4. Results

In this cohort of 74 patients, 57% were men. Mean age was 62 ± 16 years, and APACHE II score was 25.7 ± 8.5. Fifty-three percent were medical ICU admissions, and 47% were surgical admissions. In 46% of admissions, the source of infection was respiratory, whereas in 42% the source, it was abdominal, and in 12%, other sources were observed. Only 6 patients (8%) have not received hydrocortisone. This decision was taken at the discretion of the patient's physician without influence of researchers and was not related to serum cortisol concentration or response to cortrosyn test. Analysis performed with exclusion of these 6 patients has not influenced results. Blood glucose was 137 ± 45 mg/dL. Mean serum albumin was 2.0 ± 0.5 g/dL, and there was no difference between responders or nonresponders to cortrosyn. Baseline cortisol before conduction of cortrosyn test was 31.8 ± 20.3 μg/dL. In this cohort, 24% (18/74) of patients were nonresponders to the test. Cortisol variation is shown in Table 1. The variation was not related to baseline cortisol.

In the entire cohort, shock reversal was estimated in 88% of patients when KM1 method was used and 72% when KM2 method was adopted. Estimate was only 59% when CIA was used. Responders to the cortrosyn test had shock reversal estimated in 90%, according to KM1, 77% according to KM2, and 64% when analysis was performed with CIA. Among nonresponders to cortrosyn test, KM1 estimated shock reversal in 80% and 56% with KM2. The estimate was 47% when CIA was applied (Table 2 and Fig. 1).

Overall mortality on the 28th day was 57%. Mortality in nonresponders to the cortrosyn test was 61%, whereas in responders, it was 55% (log-rank P =.39). Table 3 shows the difference in estimates of shock reversal between both KM methods used and CIA and its relation to mortality. The difference is greater when KM1 is applied. In addition, it has reached 33% among nonresponders to cortrosyn, which was the group with the highest mortality rate (61%). The discrepancy between both methods is smaller (9%) when comparison is conducted between CIA and KM2.

5. Discussion

Despite that KM became the most popular method to assess time-to-event analysis in situations with competing events, it is no longer considered the most appropriate method. Our study shows that KM overestimates shock reversal in scenarios with competing events like death.

The use of stress dose steroids in patients with septic shock is partially supported by the results of trials that allowed concluding that steroids increase shock reversal [3-6]. Kaplan-Meier method has been applied in these trials, thereby leading to such conclusion. Briegel et al [3] used KM “ignoring the deaths” method; patients who died using vasopressor during follow-up were therefore considered to be alive and using vasopressor during all the follow-up period; thus, performing an estimative described in our trial as KM2. This way of censoring is the one that reaches results closer to those of CIA, but it is an “actuarial” estimated vasopressor withdrawal, and it actually estimates how many patients would exhibit shock reversal if no patients had died during the follow-up. Indeed, the most influent trials analyzing steroids and shock reversal do not mention how patients were censored. Bollaert et al [4], Annane et al [5], nor Sprung et al [6] have described how patients were censored at time of death. The authors were contacted to inform how they have censored dead patients in every trial. The authors of CORTICUS [6] have declared that they used the same methods of censoring of Briegel et al [3]. In Bollaert et al [4], authors have censored patients in the

moment of death the same way we have performed in KM1 analysis. Our study shows that this technique (KM1) is the one that most overestimates shock reversal and that the higher the mortality, the higher is the bias estimated by this technique. We did not have access to data of Annane et al [5].

Although patients can be censored in different ways [16], KM is believed to be proper for working with time for a single type of event. In this technique, the assumption of independence between event and censoring is pivotal, and it fails in scenarios with competing events. To correct the prediction of the number of patients who have actually exhibited shock reversal, it is necessary to apply a multistate model, that is, a model that deals with more than a single event and that does not assume independence between main and competing events; hence, allowing patients to present 1 event (in this case, shock reversal) without being censored to a competing event (in this case, death).

These methods are usually designated not only as CIA but also as expressions such as actual CIA or conditional probability estimation, which can be found in the medical literature. Such designations have been used by physicians in areas where competing events are usual; this can be observed in cardiac surgery (death competes with valve durability) [17,18] or oncology (death competes with disease relapse). Although competing events are common in critical care and emergency medicine, CIA has surprisingly not been as frequently applied as it should have been; recommendations support that this methodology is more appropriate though [19].

6. Conclusion

Steroid therapy in septic shock is partially supported by the statement that steroids increase shock reversal. The trials that lead to this conclusion have been applied using the KM method, and different censoring schemes were therefore used for this purpose. Our trial exemplifies that, mainly, when patients are censored in the moment of death, KM overestimates steroid influence on shock reversal. Cumulative incidence analysis is more accurate in addressing shock reversal because it addresses the actual risk of shock reversal. We hence suggest that future trials intended to analyze competing events, such as shock reversal and death, should apply CIA instead of KM.

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ARTIGO 1: Figuras e Tabelas

Table 1 Characteristics of patients

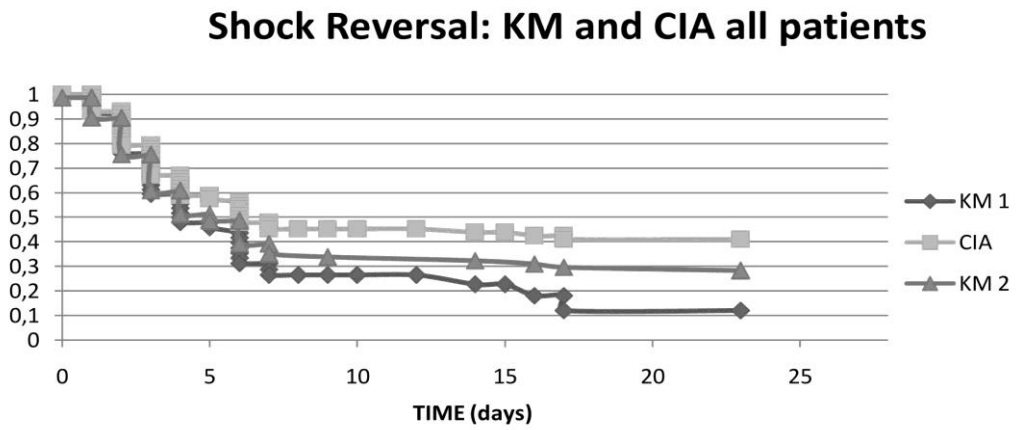
Characteristic	
Age, y	62 ± 16
Male, %	57
Admission category	
Medical, %	53
Surgical, %	47
APACHE	25.7 ± 8.5
Source of infection	
Respiratory, %	46
Abdominal, %	42
Others, %	12
Serum albumin, g/dL	2.0 ± 0.5
Blood glucose, mg/dL	137 ± 45
Baseline cortisol, μg/dL	31.8 ± 20.3
Δ Cortisol after cortrosyn test, μg/dL	
All patients	16.3 ± 10.1
Nonresponders	4.8 ± 2.8
Responders	19.9 ± 9.0
28-day mortality, %	57

Data are presented as mean ± SD.

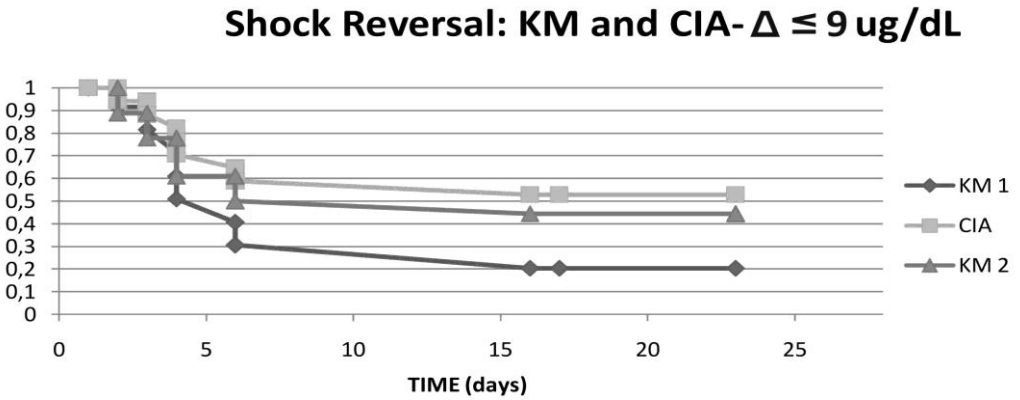
Table 2 Estimates of shock reversal according to KM methods with different censoring schemes (KM1 and KM2) and CIA in the entire cohort according to the response to cortrosyn test

Shock reversal			
	KM1 (%)	KM2 (%)	CIA (%)
All patients	88	72	59
Δ Cortisol ≤9 μg/dL	80	56	47
Δ Cortisol >9 μg/dL	90	77	64

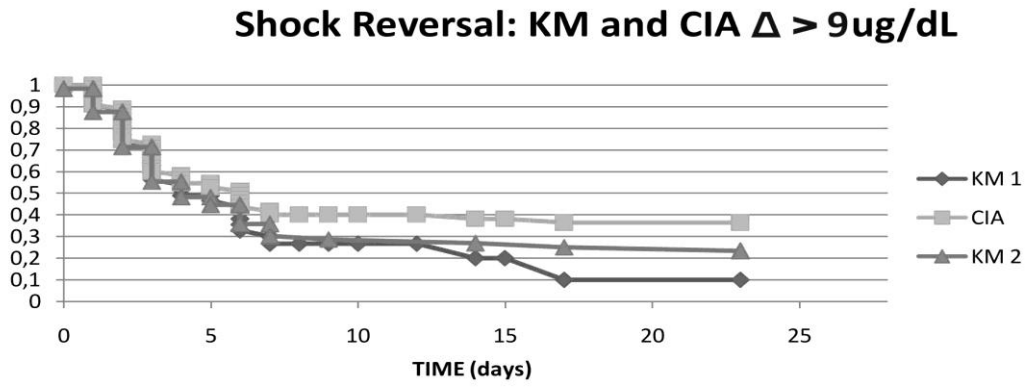
A) All patients



B) Δ cortisol ≤ 9 µg/dL



C) Δ cortisol > 9 µg/dL



KM: KAPLAN-MEIER
CIA: CUMULATIVE INCIDENCE ANALYSIS
Δ: cortisol variation

FIGURE1: Comparison of time to shock reversal between Kaplan-Meyer methods with different censoring (KM1 and KM2) and Cumulative Incidence Analysis (CIA) in the entire cohort and according to the response to cortrosyn test.

Table 3 Comparison of estimate of shock reversal between CIA and KM methods with different censoring schemes (KM1 and KM2) and relation to mortality in the entire cohort and according to the response to cortrosyn test

	Shock reversal		Mortality (%)
	Difference KM1-CIA (%)	Difference KM2-CIA (%)	
All patients	29	13	57
Δ Cortisol ≤9 μg/dL	33	9	61
Δ Cortisol >9 μg/dL	26	13	55

ARTIGO 2

Title: **Vitamin D levels and outcomes in critically ill patients: a prospective study**

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Abstract:

Introduction: Studies suggest an association between vitamin D deficiency and morbidity/mortality in critically ill patients. Nevertheless, there is insufficient data on the impact of vitamin D deficiency in this patient population. Several issues remain unexplained, such as which vitamin D levels are related with morbidity and mortality and the relevance of vitamin D kinetics to clinical outcomes. We conducted this study to address the correlation between baseline vitamin D, its kinetics, and morbidity and mortality in critically ill patients.

Materials and Methods: Observational study which prospectively allocated 135 ICU patients. Vitamin D was measured on admission and weekly until discharge from ICU. Demographic, physiologic, and laboratory data such as APACHE II score, SOFA score, and parathyroid hormone (PTH) were also analyzed. The following outcomes of interest were analyzed: 28-day mortality, mechanical ventilation, length of stay, infection rate, and culture positivity.

Results: Mortality rates were higher among patients with vitamin D levels < 12 ng/mL (32.2% vs. 13.2%; p=0.014), with a relative risk of 1.168 (95% CI 1.044–1.307). There were no differences in length of stay, ventilation requirements, infection rate, or culture positivity. Among non-survivors, 25[OH]D3 levels seems to exhibit a greater decline from the 7th ICU day onward.

Conclusions: This study suggests that low vitamin D levels on ICU admission are an independent risk factor for mortality in critically ill patients. Low vitamin D levels and vitamin D kinetics during ICU admission may have a causal relationship with mortality and serve as indicators for vitamin D replacement among critically ill patients. Randomized trials are required to confirm this hypothesis.

Keywords: Vitamin D, Septic shock, critical care, mortality

Introduction

Vitamin D is a fat-soluble vitamin synthesized in the skin in response to sunlight exposure (as provitamin D3 and previtamin D3) and, to a limited extent, from dietary intake (vitamins D2 and D3). Vitamin D is stored in adipose cells or converted in the liver to its circulating form, 25-hydroxyvitamin D3 (25[OH]D3). Mainly in the kidneys, 25[OH]D3 is converted to its active metabolite 1,25-dihydroxyvitamin D (1,25[OH]2D), also known as calcitriol. Calcitriol synthesis is enhanced by parathyroid hormone (PTH) and hypophosphatemia. The endocrine action of calcitriol on bone mineral metabolism has been known for decades, and calcitriol supplementation has been advocated in patients with chronic conditions such as osteoporosis. For many years, vitamin D deficiency was recognized as a chronic situation associated with bone pain, weakness and fractures in the general population. Serum vitamin D levels below 10 ng/mL (generally described as deficiency or severe deficiency) are associated with osteomalacia and rickets, whereas levels in the 20-30 ng/mL range (vitamin D insufficiency or subclinical deficiency) are associated with osteoporosis and elevated PTH, with the potential for long-term harmful effects on bone metabolism. Children with rickets are more susceptible to infections, and vitamin D has been implicated in the pathogenesis of tuberculosis [1-4]. The paracrine and autocrine effects of 25[OH]D3 have been increasingly reported in the literature. In recent years, it became clear that several cell lines, including macrophages and cardiac muscle cells, express the enzyme 25(OH)D3-1-alpha-hydroxylase, making them able to convert 25[OH]D3 to its active form 1,25(OH)2D, and express vitamin D receptors [5].

Studies have shown correlations between low vitamin D levels and certain types of cancer, immune system dysfunction, diabetes, cardiovascular disease, hypertension and metabolic syndrome [6-8]. Thus, investigators of several fields, including critical care medicine, have turned their attention to the nonskeletal effects of vitamin D [9]. Some observational studies have demonstrated a high prevalence of vitamin D deficiency in critically ill patients, which are generally deprived of sunlight, confined to bed and fed with low vitamin D content diets. Data about the association between vitamin D deficiency and poor ICU (intensive care unit) outcomes, such as mortality, increased length of stay, increased length of mechanical ventilation, and infections, are conflicting. The relevance of vitamin D measurement on ICU admission and of vitamin D kinetics during ICU admission is open to debate. Furthermore, the 25[OH]D3 levels required for proper maintenance of the pleiotropic effects of vitamin D are still unknown.

The purpose of this project was to study the relationship between serum levels of vitamin D on admission, vitamin D kinetics during ICU stay, and morbidity and mortality in critically ill patients.

Materials and Methods

Study design and setting: Prospective study of patients admitted to the medical-surgical ICU of a university hospital (Hospital de Clínicas de Porto Alegre, state of Rio Grande do Sul, Brazil) between March and November 2012. The city of Porto Alegre is located in the South of Brazil, at 30°05'S.The study protocol was approved by the institutional research ethics committee, and written informed consent was provided by all patients or their surrogates.

Methods: We included adult patients (age 18 years and older) with a predicted length of ICU stay greater than 3 days. We excluded patients with length of pre-ICU hospital stay > 3 days, chronic renal failure requiring dialysis or pre admission creatinine > 2 mg/dL, patients with a life expectancy of less than 24 hours, pregnant women, patients admitted for cardiac or elective surgery, patients with hyper or hypoparathyroidism, and patients with granulomatous diseases such as tuberculosis or sarcoidosis.

Patient demographic and clinical data were recorded on ICU admission, including age, sex, comorbidities, current medications, ethnicity, reason for admission, season, APACHE II score, and body mass index (BMI) (Kg/m^2). SOFA score was calculated at ICU admission and at ICU discharge or death. Infections and cultures were prospectively assessed throughout ICU stay for each patient. Infection was defined by the attending physicians, who were uninvolved with the study and had no access to serum 25[OH]D3 levels. In addition to the total number of positive cultures and clinically overt infections, the incidence rates of culture positivity and infection over time were also assessed. Patients were also assessed as to duration of mechanical ventilation, length of ICU stay, length of hospital stay, and 28-day mortality.

Biochemical analysis: Blood samples were collected within 24 hours of ICU admission for measurement of capillary blood glucose, PTH, ionized calcium, albumin, creatinine, phosphorus, magnesium, C-reactive protein, and lactate. Glomerular filtration hate was calculated using the MDRD equation [10]. All tests were performed by routine methods as employed at the biochemistry laboratory of Hospital de Clínicas de Porto Alegre. 25[OH]D3 was measured once weekly for 4 weeks or until ICU discharge. Samples were

centrifuged and stored under refrigeration until processing, which was performed once weekly on Fridays. 25[OH]D3 levels were measured using the chemiluminescence method (Liaison; Diasorin, Stillmater, Minnesota; inter- and intra-assay coefficient of variation, 10%) and reported in ng/mL [11]. (To convert 25[OH]D3 concentration from ng/mL to nmol/L, multiply by 2.5.) PTH were measured by chemiluminescent immunoassay (Advia Centaur XP; Siemens Healthcare Diagnostics Inc.).

Statistical Analysis

Normally distributed quantitative variables are expressed as mean ± standard deviation. Asymmetrically distributed variables are expressed as median [interquartile range]. The chi-square test was used for assessment of categorical variables, and the Student *t*-test, for continuous variables. Normally distributed and asymmetric variables were compared using the Mann–Whitney *U* test. Receiver-operating characteristic (ROC) curves were plotted to illustrate 25[OH]D3 cutoff values. Relative risks (along with 95% confidence intervals) were estimated using Poisson regression adjusted for 4 covariates associated with mortality: lactate, albumin, SOFA and APACHE. Survival analysis was performed by means of Kaplan-Meier curves. Log-rank statistics were used to determine significant differences over time. For comparative analysis of change in 25[OH]D3 levels over time during ICU admission between survivors and non-survivors, we used a Generalized Estimating Equation model for longitudinal data analysis [12]. Infection and culture positivity rates were compared by means of incidence density ratio analysis. The significance level was set at $p<0.05$.

Results

Cohort profile: Overall, 135 patients were allocated. The 28-day mortality rate was 21.5%. Just under half of all patients (47%) were women and 78% were Caucasian. The median vitamin D level at admission was 13.3 [8.1-20] ng/mL. Sixteen patients (11.8%) were vitamin D sufficient (25[OH]D3 > 30 ng/mL). Eighteen (13.3%) had vitamin D insufficiency (25[OH]D3 30–20 ng/mL), and 101 (74.8%) were vitamin D deficient (25[OH]D3 < 20 ng/mL). Two patients were on bisphosphonate, calcium, and vitamin D therapy prior to admission, and three were on calcium/vitamin D alone. These patients' 25[OH]D3 ranged from 4.7 ng/mL to 18 ng/mL. No patients received supplemental vitamin D during their ICU stays. The sample profile is shown in Table 1. Non-survivors had higher APACHE II and

SOFA scores, PTH, and lactate on admission, and had stormier clinical courses with more organ dysfunction (lower ΔSOFA). In addition, fewer progressed to enteral feeding; five patients were never fed due to death secondary to refractory shock within the first few days of ICU admission. Electrolytes and renal function were assessed in 117 patients who were not on dialysis at the time of 25[OH]D3 measurement. Non-survivors had lower ionized calcium levels and lower glomerular filtration rates (Table 2). Figure 1 shows the progression of vitamin D levels over time during ICU stay. Among survivors, a slight decline in 25[OH]D3 concentrations occurred over time while among non-survivors a tendency to a greater decline in 25[OH]D3 levels occurred from the 7^{th} ICU day onward.

The area under the ROC curve for 25[OH]D3 on admission related to mortality was 0.61 (95%CI 0.49–0.73), similar to those for APACHE II scores(0.7, 95% CI 0.59–0.8) and SOFA (0.7, 95% CI 0.6–0.8). The best cutoff was 11.9 ng/mL, with a sensitivity of 65%, a specificity of 62%, a negative predictive value of 86.8%, and a positive predictive value of 32.2%.

Compared to patients with 25[OH]D3 levels > 12 ng/mL, the 59 patients with 25[OH]D3 ≤ 12 ng/mL (43.7% of the sample) had higher prevalence rates of prior corticosteroid therapy (18% vs. 2.6%; p= 0.005) and of acute respiratory failure as a reason for ICU admission (25% vs. 6.6%; p= 0.013). A seasonal association was found for vitamin D deficiency (p=0.041), which was more common in the winter (37.3% vs. 21%) and less so in the summer (10.2% vs. 27.6%).Vitamin D-deficient patients had higher BMIs (27.4 [24.2–35.2] vs. 26 [22.7–29.3]; p= 0.015). There were no differences in APACHE score (19.8±9 vs. 18.7±8.3;p=0.482), SOFA score at admission (5 [2–8] vs. 5 [3–8]; p= 0.170), ionized calcium (4.7 [4.4–5.0] vs. 4.7 [4.5–4.8]; p=0.770), or PTH (146 [79–260]vs. 107 [53–200]; p=0.70), which was elevated in both groups. Patients with 25[OH]D3 levels ≤ 12 ng/mL developed greater organ system dysfunction during their ICU stays (ΔSOFA: 0.9±4.7 vs. 3.4±3.9; p=0.001).

Mortality: Over the course of the 28-day observation period, 19 of the 59 patients with 25[OH]D3 levels ≤ 12ng/Ml died (32.2%), versus 10 of the 76 patients with 25[OH]D3 levels >12ng/mL (13.2%); this difference was statistically significant (p= 0.014). The crude relative risk of death was 1.168 (95% CI 1.044–1.307). After multivariable adjustment, the relative risk remained significantly higher at 1.148 (95% CI 1.032–1.277) (Figure 2, Table 3).

There were no significant differences in mortality (23.5% vs. 15.2%; p= 0.275) when the 25[OH]D3 cutoff was set at 20 ng/mL.

Length of stay: 25[OH]D3 levels ≤ 12 ng/mL were not associated with any significant differences in overall length of hospital stay (20 [9–28] vs. 23.5 [14–28], p= 0.869) or length of ICU stay (9 [5–21] vs. 9 [5–21], p= 0.092) in days.

Mechanical ventilation: Invasive mechanical ventilation was used in 44 (74.6%) patients with 25[OH]D3 levels ≤ 12 ng/mL and 59 (77.7%) patients with 25[OH]D3 levels > 12 ng/mL (p=0.834). Survival analysis showed no differences in time on mechanical ventilation (Figure 2b).

Infection and culture positivity: Overall, 78 patients (57.8%) had positive cultures at some point during their ICU stays. Among the 59 patients with 25[OH]D3 ≤12 ng/mL, a total of 73 infections and 101 positive cultures (including 28 positive blood cultures) were detected. Among the 76 patients with 25[OH]D3 > 12 ng/mL, 88 infections and 121 positive cultures (including 32 positive blood cultures) were detected. The rates of infection and culture positivity per 100 patient-days in ICU are shown in Table 3. There were no significant differences between groups in either indicator.

Discussion

Our findings show that severe vitamin D deficiency is an independent predictor of mortality in critically ill patients. In this sample, a 25[OH]D3 level of 12 ng/mL was the best cutoff for identification of critically ill patients at higher risk of death. Weekly vitamin D measurements allowed us to observe a tendency to a dissociation between survivors and non-survivors in vitamin D kinetics; non-survivors seems to exhibit a major decline in 25[OH]D3 concentrations from the second ICU week onward.

The relationship between mortality and serum vitamin D levels in critically ill patients is a topic of debate in the current literature [13]. While some studies have reported such an association [14-21], others have found no relationship between vitamin D deficiency and mortality [22-27]. The higher mortality rate among severely vitamin D-deficient subjects found in this study is in agreement with the work of Braun et al [14-15], who found, on retrospective data collection, a relationship between 25[OH]D3 deficiency and mortality 30, 90, and 365 days after ICU admission. The limitations of this study included (1) its retrospective design, which precluded assessment of the influence of potential confounders such as APACHE and SOFA scores; (2) selection bias, as patients underwent vitamin D measure for reasons not present in the other critically ill patients; and (3) absence of data on vitamin D supplementation in the sample. Our study confirms these findings with a

prospective design and, furthermore, demonstrates that the increased mortality in critically ill patients attributed to vitamin D deficiency persists even after adjusting risk for variables usually associated with mortality in critical illness. Prospective data collection enabled calculation of APACHE and SOFA scores during the course of the ICU stay. It bears stressing that APACHE and SOFA scores on admission were similar in 25[OH]D3-deficient and non-deficient patients. Nevertheless, the mortality rate was higher in the 25[OH]D3-deficient group. No patients in our sample received supplemental calcium or vitamin D during their ICU stays. In 2012, Higgins et al [24] conducted a prospective study and found no significant differences in mortality between vitamin D-deficient and vitamin D-sufficient patients (27% vs. 22%), although deficient patients had longer ICU length of stay. The authors note that their study was not designed to assess this endpoint and was underpowered to detect differences in mortality. Heterogeneity in studies may explain different results. The Higgins et al sample was older and data collection took place between 2002 and 2003 in Canada, while our data collection took place in 2012 in Southern Brazil. In our study, we excluded patients with a total length of hospital stay of > 3 days before ICU transfer, whereas Higgins et al had no such criterion for exclusion. We thus excluded patients with normal pre-admission vitamin D levels whose decline in serum 25[OH]D3 levels was attributable to hospitalization. Our sample had a higher prevalence of sepsis as a reason for ICU admission. Some studies have suggested this etiology may be associated with higher mortality related to vitamin D deficiency [6].

Vitamin D may be no more than a marker of severity in critically ill patients. However, the literature reports several vitamin D-dependent physiologic mechanisms, which suggests that 25[OH]D3 deficiency may be implicated in the pathogenesis of organ dysfunction and mortality in critically ill patients, perhaps mediated by its effects on immunity and on the cardiovascular system. The effects of vitamin D are related to the innate and adaptive immune systems; it is responsible, among other actions, for activation of cathelicidins, endogenous antimicrobial peptides found in the mucous membranes that prevent bacterial invasion [6], helping maintain the integrity of the intestinal mucosal barrier and preventing bacterial translocation [9]. Furthermore, vitamin D levels < 10 ng/mL have been associated with heart failure mortality and sudden cardiac death [27]. As ours was an observational study, we cannot ascertain whether the association between vitamin D deficiency and mortality is causal or attributable to chance. However, even after logistic regression, 25[OH]D3 levels < 12 ng/mL remained an independent predictor of mortality.

In this study, we observed a decline in 25[OH]D3 levels in critically ill patients, with a tendency to more marked decline occurring in non-survivors. Few other studies have prospectively measured vitamin D levels during the course of an ICU stay. Higgins et al [24] restricted measurement of vitamin D levels to the first 10 days of hospitalization and did not conduct a comparative analysis of vitamin D kinetics in survivors and non-survivors. In our study, we measured 25[OH]D3 levels once weekly until the 28th ICU day and found that non-survivors experienced a non-significant decline in 25[OH]D3 concentrations after the second week in ICU. As the half-life of 25[OH]D3 is approximately 15 days, these findings partly reflect the lack of vitamin D intake during the ICU stay, due to lack of sunlight exposure and low vitamin D concentrations in the diet provided to critically ill patients. Prior studies have shown a decline in vitamin D-binding protein (VDBP) concentrations during ICU stay [28], corroborating the decline in 25[OH]D3 levels during admission, particularly in non-survivors. This behavior is analogous to that observed with other constitutional proteins, the synthesis of which is inhibited as metabolic pathways shift to the production of acute phase proteins in the setting of systemic inflammatory response syndrome (SIRS). Therefore, the criticality of the illness may also be reflected by serum vitamin D levels.

The current literature provides no information on which 25[OH]D3 levels can adequately support the pleiotropic effects of vitamin D. In our population, ROC curve analysis identified 12 ng/mL as the best cutoff for mortality. This finding is similar to one reported in a retrospective study conducted by Venkatram et al [18], in which the area under the ROC curve for mortality was 0.66 and the best cutoff was 10 ng/mL, with a sensitivity of 59.5% and a specificity of 58%. Even if 25[OH]D3 is merely a marker of severity, these studies suggest that vitamin D levels <10–12 ng/mL can be used to identify patients at higher risk of mortality and prompt more intensive monitoring of these patients. In non-critically ill patients, 25[OH]D3 levels this low are incapable of maintaining serum concentrations of 1,25(OH)2D, leading to clinical repercussions such as rickets and osteomalacia. This study suggests that, just as outpatients, critically ill patients with severe vitamin D deficiency suffer the most clinical consequences of the lack of vitamin D, from which we infer that these patients are most likely to benefit from vitamin D replacement during the ICU stay. This hypothesis must still be confirmed by clinical trials. Dietary vitamin D intakes are reduced in critically ill patients. Enteral formulas provide 200 to 300 IU/1000 mL, as do multivitamins. The current recommended daily intake of 200 IU/day is not enough to restore vitamin D sufficiency [29]. Two recent studies showed that higher (yet safe) doses are required for vitamin D replacement in critically ill patients. In the first such study [30], two doses of

60,000 IU each were provided via the enteral route. In the second study, a single 540,000-IU dose was found to be safe [31]. We are currently awaiting the results of two intervention studies designed to assess clinical outcomes after vitamin D supplementation in critically ill patients. In the first (ClinicalTrials.gov, NCT01130181), a randomized, double-blind, placebo-controlled clinical trial, critically ill patients received a loading dose of 540,000 IU of cholecalciferol via feeding tube or orally, then 5 monthly doses of 90,000 IU. This study has already been completed but results are not currently available. A phase 2 trial (ClinicalTrials.gov, NCT01372995) comparing doses of vitamin D (50,000 IU vs. 100,000 IU vs. placebo, for 5 days) is at the patient recruitment stage.

As in other prospective studies [24, 32], we found no significant differences in infection and culture positivity rates between vitamin D-deficient and non-deficient patients. Previous studies have shown a trend toward greater incidence of infections, but have lacked statistical power to establish this association conclusively. Higher rates of infection and culture positivity have been observed among 25[OH]D3-deficient patients in retrospective studies [14], which, despite design bias, are able to allocate larger samples. Definitive assessment of the potential association between vitamin D deficiency and infections may require a meta-analysis of published data.

Although the literature suggests an association between 25[OH]D3 deficiency and morbidity in critically ill patients, out study did not find longer duration of mechanical ventilation among patients with severe vitamin D deficiency. These results are consistent with other recently published prospective studies conducted in adult [17, 18, 21] and pediatric [26] critically ill populations.

The high prevalence of vitamin D deficiency and insufficiency observed in our sample is consistent with other studies carried out at other centers, as well as with the high prevalence found in the non-critically ill population in our midst [33]. We are unaware of other reports of the prevalence and incidence of vitamin D deficiency in critically ill patients in South and Central America.

This study has some limitations. It was conducted at a tertiary care center with a largely Caucasian population, thus limiting generalization of findings to other settings or samples. As a relatively small number of patients were allocated, we cannot rule out associations between vitamin D deficiency and endpoints such as length of stay, mechanical ventilation, or hospital-acquired infection. The infection rate was calculated solely on the basis of clinical diagnoses made by the assisting physicians. We cannot rule out completely the potential influence of unassessed variables—such as volume infused in the first hours after

admission—on mortality [34]. VDBP and biologically active 25[OH]D3 metabolites were not measured. It bears stressing that the pleiotropic effects of vitamin D are dependent on local vitamin D concentrations; it is biologically plausible that these effects would be independent of serum 25[OH]D3 levels. Furthermore, the association between mortality and severe vitamin D deficiency found in this observational study is not enough to recommend measurement of vitamin D levels in critically ill patients or supplementation in those with vitamin D deficiency; such changes in practice would depend on the results of clinical trials, which are ongoing.

The strengths of this study include assessment of a hard endpoint (mortality) not prone to measurement bias. In addition to 25[OH]D3 levels, we measured other components that affect the vitamin D axis, such as PTH, ionized calcium, magnesium, and phosphorus. The method employed for 25[OH]D3 measurement was the DiaSorin radioimmunoassay, which is currently considered the gold standard for this purpose in view of its excellent agreement with isotope dilution liquid chromatography-tandem mass spectroscopy (LC-MS) [13, 35]. We did not measure 25[OH]D3 only at admission, but also during the course of the ICU stay. Prospective once-weekly monitoring of serum vitamin D levels in the ICU allowed us to control for some potential confounders of mortality, including APACHE and SOFA scores, lactate, and albumin.

Conclusions

This study found that low vitamin D levels on admission are an independent risk factor for mortality in critically ill patients and that non-survivors exhibited precipitous declines in vitamin D levels while in the ICU. The best cutoff of 25[OH]D3 levels on admission for stratification of risk of death among critically ill patients was 12 ng/mL. As well as being markers of disease severity, low vitamin D levels and vitamin D kinetics during ICU admission may be causally associated with mortality and serve as indicators for vitamin D supplementation in this patient population. Nevertheless, randomized trials are required to confirm this hypothesis.

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Conflict of interest: The authors declare no conflict of interest

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ARTIGO 2: Figuras e Tabelas

Table 1: Sample profile

	Survivors (n=106)	Non-survivorsn=(29)	*P*
Age, years	55.4±16.1	60.4±16.6	0.141
Gender, n(%)			0.462
- female	48 (45%)	16 (55%)	
- male	58 (55%)	13 (45%)	
Comorbidities, n(%)			
- Coronary artery disease	12 (11.3%)	3 (10%)	0.882
- Hypertension	54(51%)	14 (48%)	0.964
- Heart failure	13 (12%)	3 (10%)	1.000
- Diabetes	27 (25%)	6 (21%)	0.774
- Hypothyroidism	3 (2.8%)	3 (10%)	0.113
- Chronic renal failure	3 (2.8%)	1 (3.4%)	1.000
- COPD	19 (18%)	5 (17%)	1.000
- Asthma	4 (3.8%)	3 (10%)	0.169
- AIDS	8 (7.5%)	0	0.201
- Cirrhosis	9 (8.5%)	3 (10%)	0.720
- Stroke	7 (6.6%)	4 (14%)	0.249
- Depression	8 (7.5%)	0	0.201
- Neoplasia	14 (13%)	5 (17.2%)	0.557
- Other	20 (19%)	7 (24%)	0.714
Chronic medications, n(%)			
- Diuretic	28 (26.4%)	11 (38%)	0.326
- Corticosteroid	8 (7.5%)	5 (17%)	0.125
- Ca/VITD	3 (2.8%)	2 (7%)	0.292
- Bisphosphonate	1 (1%)	1 (3.4%)	0.385
- Antiepileptic	4 (3.8%)	3 (10.3%)	0.169
- Proton pump inhibitor	10 (9.4%)	1 (3.4%)	0.456
Ethnicity, n(%)			0.660
- Caucasian	83 (78.3%)	22 (75.9%)	
- African	14 (13.2%)	3 (10.3%)	
- Other	9 (8.5%)	4 (13.8%)	
Reason for ICU admission, n(%)			0.009
- Sepsis	34 (32%)	14 (48%)	
- Acute respiratory failure	17 (16%)	3 (10%)	
- Post surgery	5 (4.7%)	1 (3.4%)	
- Post cardiac arrest	4 (3.8%)	1 (3.4%)	
- Coma	4 (3.8%)	5 (17%)*	
- Non-septic shock	4 (3.8%)	3 (10%)	
- Acute renal failure	4 (3.8%)	0	
- Other	34 (32%)*	2 (7%)	
Provenance, n(%)			0.839
- Emergency department	73 (69%)	21 (72%)	
- Ward	2 (1.9%)	0	
- Operating room	11 (10%)	2 (7%)	
- Other	20 (30%)	6 (20.7%)	

Admission service, n(%) - Medical - Surgical	 80 (75%) 26 (25%)	 21 (72%) 8 (28%)	0.924
Season of admission, n(%) - Summer - Autumn - Winter - Spring	 23 (22%) 36 (34%) 28 (26%) 19 (18%)	 4 (14%) 8 (27.5%) 10 (34.5%) 7 (24%)	0.577
APACHEII score	17 [12 to 23]	23 [18 to 29]	0.001
SOFA score	4.5 [2 to 8]	7 [4.5 to 12]	0.001
ΔSOFA	3.0 [1 to 6]	-2 [-5.5 to 1.5]	0.001
BMI (Kg/m^2)	26.7 [23.3 to 30.5]	26.5 [23.5 to 31.6]	0.823
Capillary blood glucose (mg/dL)	146 [113 to 193]	141 [99 to 189]	0.485
Albumin (g/dL)	3.1±0.6	2.7±0.8	0.004
CRP(mg/L)	83 [28 to 231]	168 [23 to 264]	0.316
Lactate(mmol/L)	1.4 [1 to 2.1]	3.1 [1.4 to 5.6]	0.001
PTH (pg/mL)	97.9 [56.8 to 198.6]	200.8 [92.6 to 331]	0.023
Nutrition, n(%) - Oral/enteral - Parenteral - None	 104 (99%)* 1 (1%) 0	 22 (78.6%) 1 (3.6%) 5 (17.9%)*	<0.001

COPD: chronic obstructive pulmonary disease; Ca/VITD: calcium/vitamin D ratio; ΔSOFA: SOFA on admission -final SOFA (at ICU discharge or death); BMI: Body Mass Index (Kg/m^2); CRP: C-reactive protein; PTH: parathyroid hormone. * denotes statistically significant change.

Table 2: Electrolyte levels and renal function of patients not on acute dialysis at the time of laboratory testing.

	Survivors (n=95)	Non-survivors (n=22)	*p*
Ca^{++}(mg/dL)	4.7 [4.6-4.9]	4.4 [3.8-4.7]	0.001
GFR (mL/min/ 1.73 m^2)	60 [48-60]	59 [26-60]	0.042
Phosphorus (mg/dL)	2.9 [2.3-4.2]	3.2 [2.7-4.3]	0.334
Magnesium (mg/dL)	2.0 ± 0.4	1.9 ± 0.36	0.345

GFR: glomerular filtration rate calculated by MDRD (Modification of Diet in Renal Disease Study Group). Values expressed as total mean ± confidence interval OR median [interquartile range].

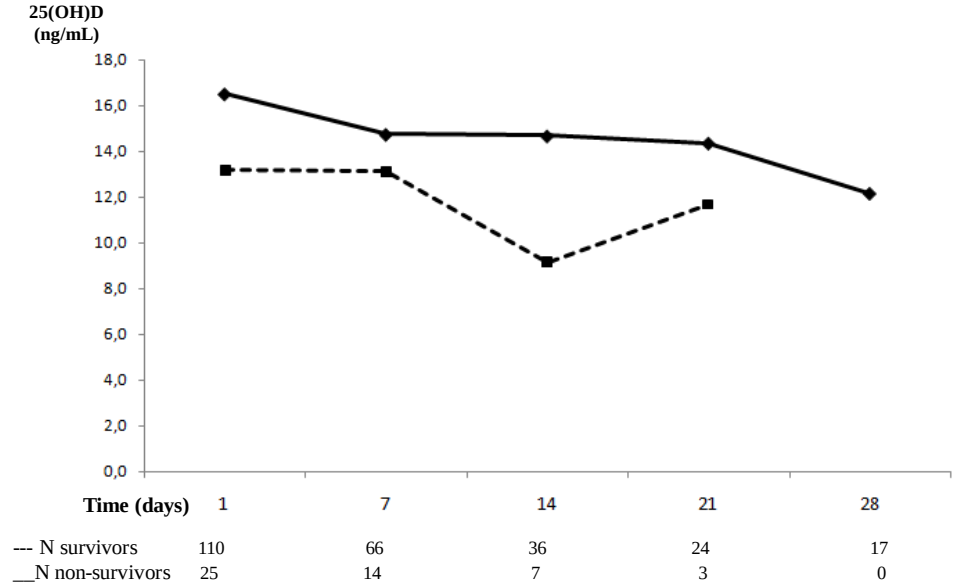
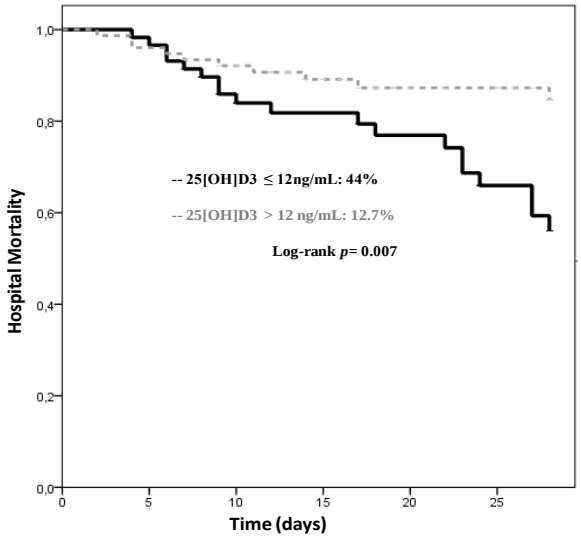


Figure 1. Vitamin D (25(OH)D3) levels throughout ICU stay in survivors and non-survivors. N: number of patients.
To convert 25[OH]D concentration from ng/mL to nmol/L, multiply by 2.5

2a) 28-day mortality



2b) Mechanical ventilation

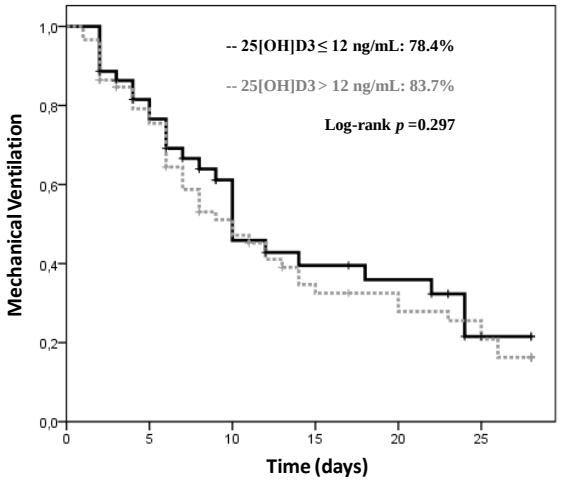


Figure 2: Kaplan–Meier curves showing 28-day survival and mechanical ventilation rate in patients with and without severe vitamin D deficiency (≤12ng/mL).

Table 3: Mortality, mechanical ventilation and culture positivity according to vitamin D (25[OH]D3) status

	25[OH]D3 ≤ 12ng/mL	25[OH]D3 >12ng/mL	*P*
28-day mortality, %	32.2	13.2	0.014
Mechanical ventilation,%	74.6	77.4	0.834
Infections*	10.08	8.98	0.468
Positive cultures*	13.95	12.35	0.369
Positive blood cultures*	3.86	3.26	0.516

ICU: Intensive Care Unit

*Rate of events per 100 patient-days in ICU

CONSIDERAÇÕES FINAIS E PERSPECTIVAS

Há muito a ser compreendido sobre o funcionamento do sistema endocrinológico em pacientes críticos e a colaboração entre intensivistas e endocrinologistas é fundamental neste processo. A colaboração entre Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grando do Sul, Serviço de Medicina Intensiva e Programa de Pós Graduação em Endocrinologia tem contribuido na construção do conhecimento científico neste campo. É neste contexto que inserimos nossa linha de pesquisa em endocrinologia do paciente crítico.

No primeiro estudo desta tese mostramos o quão instável é a base na qual se sustenta o uso de esteróides em portadores de choque séptico. Em consonância com nossos resultados, causam preocupação os recentes levantamentos que evidenciam que a forma atual como esteróides são empregados no choque séptico se associa com maior mortalidade (1). A maioria dos intensivistas atualmente defende a prescrição de hidrocortisona para pacientes em choque séptico dependente de vasopressores. Cada vez menos os pesquisadores têm focado seus estudos no uso de esteróides em portadores de disfunção adrenal relacionada à doença crítica. Parte deste descrédito se deve a incapacidade do teste de cortrosina em alta dose em identificar de forma dinâmica e completa o eixo hipotálamo- hipófise- adrenal. Entendemos que enquanto não dispusermos de métodos diagnósticos que se adequem a dinamicidade das alterações hormonais observadas no paciente crítico (em oposição a estabilidade observada no ambiente de atendimento ambulatorial) dificilmente conseguiremos adequar terapêutica.

Na última década diversos autores têm sugerido o emprego do termo *Critical Illness-Related Corticosteroid Dysfunction (CIRCI)* em detrimento do termo Insuficiência Adrenal Relativa (IAR) (2). Esta nova nomenclatura (*CIRCI*) agrega um conceito importante: a resistência periférica à ação do cortisol. Assim como observamos com outros hormônios, a doença crítica aguda cursa com resistência pelos tecidos alvo à ação dos esteróides, potencialmente causando ação insuficiente mesmo com produção hormonal adequada. O impacto da resistência tecidual à ação dos esteróides na mortalidade do paciente crítico e o método de avaliá-la ainda demandam mais estudos (3,4).

Outro ponto que julgamos deva ser explorado em futuros ensaios é o papel da zona glomerulosa da adrenal. Nesta zona ocorre a produção de aldosterona, responsável por retenção de sódio e consequentemente de água, contribuindo relevantemente para manutenção de perfusão orgânica. A disfunção na produção de aldosterona em pacientes críticos foi pela

primeira vez descrita nos anos 1980 (5) recebendo a denominação de Hipoaldosteronismo Hiperreninêmico, tendo sido pouco estudada até o momento. Alguns estudos sugerem associação entre Hipoaldosteronismo Hiperreninêmico e mortalidade em pacientes críticos (6). Recentemente concluímos estudo observacional onde investigamos a ativação da zona glomerulosa em pacientes com choque séptico. Nossos resultados sugerem que Hipoaldosteronismo Hiperreninêmico possa estar mais fortemente associado à mortalidade no choque séptico que a disfunção na produção de cortisol, podendo futuramente constituir-se em alvo terapêutico (7). Neste campo entendemos ainda serem necessários maiores estudos observacionais que definam critérios diagnósticos desta alteração para embasar ensaios clínicos randomizados que investiguem a reposição de hidrocortisona em pacientes críticos com Hipoaldosteronismo Hiperreninêmico. Atualmente a relação aldosterona/ renina < 2 é sugerida como critério diagnóstico para definição de Hipoaldosteronismo Hiperreninêmico.

O segundo estudo que faz parte desta tese avalia o papel da vitamina D em pacientes críticos. Neste estudo prospectivamente acompanhamos os níveis de vitamina D durante internação em UTI. Encontramos associação entre deficiência severa de vitamina D e mortalidade em pacientes críticos, a qual permanece mesmo após emprego de regressão logística. Identificamos ponto de corte de vitamina D com maior associação com mortalidade e descrevemos o significativo declínio das concentrações de vitamina D ao longo da internação em UTI entre pacientes com evolução ao óbito, em oposição aos sobreviventes. Entendemos que nossos resultados apresentam relevância para nosso meio por narrar a alta prevalência de deficiência de vitamina D em nossas UTIs. Entendemos também que estes resultados podem embasar futuros ensaios clínicos randomizados que abordem a reposição de vitamina D em pacientes críticos.

O papel da vitamina D no paciente crítico deverá ser tema bastante assíduo na literatura de endocrinologia e medicina intensiva nos próximos anos (8). Entendemos ainda serem necessários mais estudos observacionais que elucidem que níveis séricos de vitamina D se relacionam com sua atividade pleiotrópica. É possível que o benefício do uso de vitamina D não seja universal entre pacientes críticos, mas, se presente, restrito a algumas subpopulações, como pacientes com sepse, portadores de patologias de vias aéreas, portadores de deficiência de vitamina D á internação em UTI ou que evoluem com deficiência ao longo da internação. São necessários mais estudos que avaliem a cinética da vitamina D ao longo da internação em UTI em diversos centros e que tenham poder para avaliar subpopulações específicas como as previamente citadas. Estes resultados são indispensáveis para que no futuro possamos ter uma posição sobre a necessidade de aferir seriadamente as concentrações de vitamina D entre

pacientes críticos e em realizando estas medições, que intervalo deve ser observado entre estas aferições. Entendemos que os resultados destes estudos observacionais são fundamentais para correta leitura dos ensaios clínicos que pretendem avaliar a suplementação de vitamina D nesta população. Atualmente aguardamos os resultados de dois ensaios clínicos que investigam o papel da vitamina D em pacientes críticos. O primeiro deles estudou a suplementação de altas doses de vitamina D. Embora o ensaio tenha encerrado a fase de alocação de pacientes, ainda não há relatos de seus resultados (ClinicalTrials.gov, NCT01130181). Outro estudo, de fase 2, atualmente em fase de alocação de pacientes tem como objetivo comparar diferentes doses de suplementação de vitamina D em pacientes críticos (ClinicalTrials.gov, NCT01372995). Apesar disso a definição sobre suplementação de vitamina D em pacientes críticos dependerá da realização de ensaios clínicos multicêntricos adequadamente delineados.

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