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Enteral Nutritional Therapy in the Critically Ill Patient Using Vasopressors

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Abstract

Introduction: Early Enteral Nutritional (EN) therapy can contribute significantly to reducing mortality in critically ill patients, but the indication for its initiation may be controversial in patients using vasopressors. Vasoactive drugs may contribute to intolerance of ET due to inadequate perfusion and poor splanchnic circulation, which favors the risk of mesenteric ischemia. The objective of this work was to review the possibilities, benefits and risks of early enteral nutrition therapy in critically ill patients using vasopressors.

Methods: A literature review of scientific articles was carried out in the Scielo, Lilacs, Capes, PubMed databases, using the main descriptors: "Enteral nutrition", "critical care", "vasopressors", "intensive care unit", "early enteral nutrition", considering the period from 2009 to 2020. The languages English, Portuguese and Spanish were considered. Inclusion criteria considered critically ill patients over 18 years of age, clinical or surgical, using vasopressor agents alone or associated, with or without use of Extracorporeal Membrane Oxygenation (ECMO). A total of 14 articles were selected according to the pre-established inclusion criteria. Observational, retrospective, prospective studies and randomized controlled trials were included. Type of study, patient profile, the association between enteral nutrition and use of vasopressors and the outcome were evaluated. Studies that evaluated mortality and length of stay and mechanical ventilation time were also analyzed.

Results: It is observed through the studies, that the use of enteral nutrition therapy for the critically ill patient using vasopressors can bring benefits for nutritional supply, preservation of the gastrointestinal tract, contributing to a reduction in mortality, mechanical ventilation time and length of hospital stay. However, we know that more analyses and studies are required for further conclusions.

Conclusion: Early EN is possible and indicated in most critically ill patients using vasoactive drugs in stable and decreasing doses, with adequate parameters of tissue perfusion.

Keywords: Enteral nutrition; Vasopressors; Vasoconstrictors; Intensive care unit

Introduction

The critically ill patient is the one who presents instability or risk of instability of a vital system with risk of death. This individual requires several types of therapeutic interventions that contribute to better outcomes, among them nutritional therapy, which is an essential factor in this care. Evidence suggests that patients with an intact gastrointestinal tract should preferably receive EN, benefiting from an early start whenever possible [1-4].

Studies have shown that the use of early enteral nutritional therapy in critically ill patients using vasopressors has benefits with no association with hemodynamic changes, in addition to providing protection and preservation of the gastrointestinal mucosa and immunological improvement [5-8].

The gastrointestinal tract is recognized for playing an integral role in the pathophysiology of critically ill patients. In this condition it presents important alterations as it undergoes changes in its epithelial homeostasis, increased production of pro-inflammatory cytokines, dysfunction of the intestinal barrier and cell apoptosis, contributing to a higher risk of multiple organ failure [5,6].

In Intensive Care Unit (ICU) vasoactive drugs are frequently used, requiring from the intensivist, full knowledge of their pharmacokinetics and pharmacodynamics when prescribing them, to ensure their successful use. These substances present peripheral vascular, pulmonary or cardiac effects, direct or indirect. The most used vasoactive drugs are catecholamines, also called vasoactive amines or sympathomimetic drugs. Among them, noradrenaline, adrenaline, dopamine, dopexamine, dobutamine and isoproterenol stand out. Milrinone and vasodilators (sodium nitroprusside, nitrates, chlorpromazine, prazozin, captopril, enalapril and calcium blockers) can also be used [6,9].

These drugs act mainly on parameters that regulate cardiac output. Among the main objectives of using these substances is the optimization of oxygen supply due to altered metabolic demand of different organs and tissues in an attempt to preserve cellular biochemical function. Studies in patients with cardiogenic shock show that the use of early enteral nutritional therapy in the postoperative period of cardiac surgery using

vasopressors may increase the cardiac and splanchnic blood flow, preserving the intestinal absorption capacity [1,6,9].

Early administration of enteral nutrition favors the prevention of intestinal mucosa atrophy, being called trophic nutrition when used in low volume and with benefits in stimulation of enzyme secretion, improvement of immune function and prevention of bacterial translocation, even not meeting the total daily caloric needs of the patient [3,5,8]. Clinically, when appropriately prescribed, early enteral nutrition significantly reduces mortality of ICU patients under mechanical ventilation [1,3,10].

It is currently recommended to wait for the start of parenteral nutrition in patients with hemodynamic instability requiring support with vasopressors. Guidelines of the American Society of Parenteral and Enteral Nutrition (ASPEN, 2016), European Society for Clinical Nutrition and Metabolism (ESPEN,2019) and the Brazilian Guideline of Nutritional Therapy in the Critically Ill Patient (BRASPEN, 2018) suggest that nutritional therapy be initiated under hemodynamic stability, and if necessary, that it be interrupted until the patient is completely stable [1,6,7,11,12].

The aim of this study was to perform a review on the possibilities, benefits and risks of the use of early enteral nutritional therapy in critically ill patients using vasopressors.

Methodology

A literature review of scientific articles was carried out in the Scielo, Lilacs, Capes, Pubmed databases, using the main descriptors: "Enteral nutrition", "critical care", "vasopressors", "intensive care unit", "early enteral nutrition" considering the period from 2009 to 2020. The languages English, Portuguese and Spanish were considered.

The inclusion criteria considered critically ill patients over 18 years of age, clinical or surgical, using vasopressor agents alone or associated, with or without cardiopulmonary bypass ECMO. A total of 14 articles were selected according to the pre-established inclusion criteria. Observational, retrospective, prospective studies and randomized controlled trials were included.

Type of study, patient profile, the association between enteral nutrition and use of vasopressors and the final outcome were assessed.

The doses of vasopressors associated with the use of enteral nutrition were evaluated. The studies that evaluated mortality and length of stay and mechanical ventilation time were also analyzed.

Results

The data presented in **Table 1** show that there is a possibility of introducing enteral nutritional therapy in hemodynamically stable critically ill patients using low doses of vasoactive drugs [8,13-16].

Table 1: Analysis of clinical studies and tolerance to enteral nutrition therapy in critically ill patients using vasopressors.

Author	Year	Type of study	Patient profile	Key points
Evy, et al.	2020	Observational retrospective	EN, MV and (vasopressors)	Early EN in septic shock was not associated with worsening of hemodynamic instability. The median dose variation over 0 to 6 hours was 0.85 µg/kg/min
Patel, et al.	2019	Randomised controlled, centralised	EN, MV and vasopressors	Early trophic EN may be beneficial in the population with vasopressors at a dose of 0.08 µg/kg/min
Ohbe, et al.	2019	Observational retrospective	EN (early x late), MV and vasopressors	Patients with 'controlled' shock requiring low or medium dose (<0.3 µg/kg/min) noradrenaline benefited from early EN
Reigner, et al.	2018	Controlled, randomized multicenter	EN, PN, MV and vasopressors	Early NES did not show greater benefit than early PN for normocaloric target, NES showed greater risk of complications with doses

				of 0.25 µg/kg/min to 1.20 µg/kg/min of norepinephrine
Ohbe, et al.	2018	Observational retrospective	EN, (ECMO) (vasopressors)	Early EN seems to be associated with lower mortality in VAD of 0.03 µg/kg/min to 0.1 µg/kg/min norepinephrine
Merchan, et al.	2016	Observational retrospective	EN, MV and vasopressors	Early EN has proven safe in hemodynamically compensated patients. Equivalent doses <0.14 µg/kg/min of norepinephrine
Lasierra, et al.	2015	Observational prospective	EN, MV and vasopressors	The start of EN was viable, but with lower energy supply evolution at doses of norepinephrine 0.23-0.41 µg/kg/min; dobutamine 5.33-9.05 mcg/kg/min, dopamine 4.71-7.99 mcg/kg/min
Patel, et al.	2014	Observational retrospective	EN, MV and vasopressors	Septic shock patients who received <600 kcal in the first 48 h/day *via* EN had shorter duration of mechanical ventilation and shorter ICU stay.
Mancl, and Muzevich	2013	Observational retrospective	EN, MV and vasopressors	Demonstrated hemodynamic improvement after initiation of NE. Doses used: Minimum 0.09 µg/kg/min maximum dose 0.23 µg/kg/min norepinephrine
Makikado, et al.	2013	Observational retrospective	EN, (ECMO/ vasopressors)	Early EN was possible and safe under appropriate medical supervision 0.13 µg/kg/min to 1.60 µg/kg/min norepinephrine
Rice, et al.	2012	Randomized multicenter (open-label)	EN, MV and vasopressors	Trophic EN did not significantly reduce mortality, but reduced length of hospital stay and was associated with less gastrointestinal intolerance

Rice, et al.	2011	Randomised multicentre (open-label)	EN and MV, 1/3 of patients using vasopressors	Patients on initial trophic EN and full EN with mechanical ventilation showed good tolerance, with similar results
Khalid I, Doshi P, DiGiovine B	2010	Observational retrospective	EN, MV and vasopressors	Lower mortality in the group with early EN and associated vasopressor drugs (use of multiple vasopressors)
Berger MM, et al.	2005	Observational prospective	post critical surgery/ EN or PN and vasopressors	The start of the trophic EN was possible

Not all studies evaluated specify the doses of vasoactive drugs used, but those that do, cite values between 0.14 µg/kg/min of norepinephrine to <0.3 µg/kg/min of norepinephrine [8,16]. The introduction of parenteral nutrition has been found to reduce mortality and length of hospital stay [13,17,18].

Considering the challenge to achieve nutritional goals in the ICU due to slow progression of enteral nutrition therapy. Studies have shown that patients receiving hypocaloric enteral nutrition in the first 48 hours had shorter mechanical ventilation and ICU stay [13,19,20].

It can be observed through the studies that there is a positive response to the use of enteral nutritional therapy in these conditions, being a benefit for the critically ill patient, contributing to reduce mortality, mechanical ventilation time and length of stay. However we know that further analyses and studies are required for more conclusions [5-8,10,20].

Contraindication for enteral nutrition as evidenced by literature recommendations is in hemodynamically unstable patients, with unreachable tissue perfusion levels and high lactate doses [1,2,12,21].

Discussion

Based on expert consensus, nutrition societies suggest that in case of hemodynamic impairment or instability, PN should be discontinued until the patient is fully resuscitated and/or stable. The major concern with nutrition therapy in patients on vasopressors is the risk of non-occlusive intestinal ischemia. As recently reported, the rate of occurrence of intestinal ischaemia and non-occlusive intestinal ischaemia ranges from 0.3% to 8.5%, with mortality ranging from 46% to 100% [1,6,7,12,22]. The initiation or reintroduction of Parenteral Nutrition (PN) may be considered with caution in patients undergoing withdrawal or reduction of vasopressor support.

The study by OHBE, et al. 2018, considered 1769 patients studied for 69 months, using mechanical ventilation, ECMO and vasoactive drugs noradrenaline, dobutamine and vasopressin with doses ranging from 0.03 µg/kg/min to 0.1 µg/kg/min. When analyzing two groups of patients, those who started nutritional therapy early and those who started late, they observed that 28-days mortality was significantly lower in patients who had enteral nutrition therapy. In agreement, in the study by Khalid, et al. patients using multiple vasopressors who received early enteral nutrition had lower in-hospital mortality compared to the group with enteral nutrition started late. Rice, et al. 2012, found no significant differences on mortality when analyzing trophic enteral nutrition or full enteral nutrition, during the period of 60 days in patients under use of vasopressors [13,17,18].

In the criterion of length of stay, Patel and collaborators in 2014 analyzed patients on mechanical ventilation in septic shock conditions and use of vasopressors. The length of stay in ICU was shorter in the group that received lower volume of enteral nutrition in the first 48 hours [10]. In another study 52,563 patients were investigated for 69 months, considering the slopes of low dose of noradrenaline <0.1 µ/kg/min, medium dose between 0.1 to 0.3 µ/kg/min and with high dose >0.3 µ /kg/min. There were no statistical differences regarding the duration of mechanical ventilation, but regarding the 28 days mortality, the low dose noradrenaline and early PN group presented significantly lower values compared to the high dose noradrenaline with early or late enteral nutrition group [16].

Evy, et al. when studying patients with a median variation of noradrenaline use for 0 to 6 hours 0.85 µg/kg/min, and in use of enteral nutrition for a mean of 60.5 hrs, identified that the dose of vasopressors did not change in the first 24 hrs while associated with the use of enteral nutrition, suggesting that the beginning of nutritional therapy during septic shock did not contribute to the worsening of instability, but this work is constituted of a small sample [15].

Patel, et al. studied patients on early versus fasting nutrition therapy, at a mean dose of 0.08 µg/kg/min of noradrenaline. In the early nutrition therapy group there were more days free of mechanical ventilation and earlier ICU discharge compared to the group without enteral nutrition. Hospital mortality was 2% compared to 6% in the group not using nutritional therapy [23].

In Merchan's analysis, patients using enteral nutrition and vasopressors, 62% had good tolerance to enteral nutrition therapy and there were no reports of mesenteric ischemia. The authors showed that the use of early nutrition therapy, in the first 48 hrs, using vasopressors at a dose of up to 0.14 µg/kg/min

of norepinephrine, presented good tolerance of nutritional therapy [8].

According to the work by Mancl and collaborators, 259 patients in associated use of enteral nutritional therapy and vasopressors were evaluated, it was observed that patients who never received vasopressin had better tolerance to nutritional therapy compared to those who were receiving it (77.9% *vs* 58.9%), as well as regarding dopamine, patients who never received it tolerated nutritional therapy better (77.6% *vs* 63.8%). Overall tolerability of enteral nutrition was 74.9%. Some adverse events included increased serum lactate (30.6%), high gastric residual volume (14.5%), emesis (9.0%), positive renal/ureter/bladder X-ray findings (36.6%) and intestinal ischaemia or perforation (0.9%). There is an inverse relationship between the maximum dose of norepinephrine equivalent and tolerance [10].

In the NUTRIREA study intensive care patients under mechanical ventilation and using vasopressors in doses from 0.25 mcg/kg/min to 1.20 mcg/kg/min of norepinephrine were evaluated. Patients were divided in two groups, those who used enteral nutrition and those who used parenteral nutrition therapy. There were no statistically significant differences regarding infection in the enteral group versus the parenteral group [24].

In the ICU environment, one of the major challenges is to reach nutritional goals, due to the need of slowly progressing enteral nutrition therapy. Studies have shown that patients receiving hypocaloric enteral nutrition in the first 48 hrs had shorter duration of mechanical ventilation and ICU stay [13,19,21]. The study by Berger, et al. evaluated patients in the postoperative period of cardiac surgery with use of cardiopulmonary bypass and enteral nutrition. The energy supply ranged between 35% and 70% of the estimated needs. One of the reasons was the negative influence of the higher doses of norepinephrine and dopamine, preventing the administration of full nutrition [19]. In the study by Lasierra, et al. stable post heart surgery patients were maintained on two or more vasoactive drugs or mechanical circulatory support. The energy goal was achieved in only 40% of the patients, while 92% showed good tolerance to EN [21].

Makikado and collaborators, in a prospective observational analysis carried out in a surgical ICU, observed that patients using ECMO and noradrenaline in doses between 0.1 and 1.6 µg/kg/min, presented 70% of EN tolerance, achieved in the first week in all cases and without serious adverse effects. The study suggested that early enteral nutrition in patients on vasoactive drugs may be effective and safe [14].

According to the recommendations presented by BRASPEN, ESICM, ESPEN and ASPEN we identify the priority to start nutritional therapy with the patient hemodynamically stable, observing and monitoring tolerance [1,2,12,21]. In stable patients with decreasing doses of vasoactive drugs, enteral nutrition should be started as soon as possible, with caution, monitoring any intolerance or presence of gastrointestinal symptoms and starting at low volume (10 ml-20 ml/hr). Priority should be given to postpone the start of enteral nutritional therapy if hemodynamic instability and tissue perfusion levels are not reached, starting as soon as possible at low volume when hemodynamic control is present, paying attention to high noradrenaline and lactate doses [1,2,12,21].

Conclusions

Initiation of early enteral nutritional therapy is possible and may be indicated under use of vasoactive drugs in stable doses and adequate tissue perfusion parameters.

Malnutrition in critically ill patients is a pre-existing disease and contributes to several complications compromising the patient's outcome, at all moments from the beginning at admission, in the acute phase until the post-ICU phase and hospital discharge. For these reasons, early nutritional therapy is something that must be optimized and valued, in the sense of ensuring the best recovery and prevention of weakness acquired in the ICU, enabling the patient to resume as soon as possible his/her activities, work and life normally after discharge and recovery.

We know that facing so many challenges in the situation of the critically ill patient, to nourish and reach the nutritional goals may be a difficult task and requires a complete nutritional assessment, daily analysis and re-evaluation of the patient, understanding his current moment, as well as his clinical, hemodynamic and emotional situation, in order to safely prescribe nutritional therapy and ensure its good tolerance according to each patient's phase.

The nutritional planning outlined by the dietitian should always be shared in a multidisciplinary visit, seeking a good alignment in the nutritional care also by the team. The knowledge of the clinical and hemodynamic moment of the critically ill patient is fundamental so that nutritional prescription and planning can be safely applied.

Conflict of Interest

No conflict of interest.

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