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Original Article

Administration of enteral nutrition and gastrointestinal complications in Covid-19 critical patients in prone position

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SUMMARY

Background: The prone position (PP) used in the treatment of critically ill patients infected with SARS-CoV-2, may be a barrier to enteral nutrition (EN). This study aimed to analyze the effectiveness and complications of EN in the PP, as well as clinical outcomes.
Methods: Prospective cohort study with patients in EN and coronavirus disease 2019 (COVID-19), on mechanical ventilation (MV), which whom needed or not PP. Gastrointestinal intolerances (GII) related to PP were evaluated, and correlated with possible confounding factors. EN, days on MV, Intensive Care Unit (ICU) length of stay, hospital length of stay, ventilator-associated pneumonia (VAP) and mortality were analyzed. The data were evaluated daily and compared prone group (PG=57) and supine group (SG=69).
Results: The PP was associated with GII (P=0.000) and presented in 32 patients (26,44%) with no difference among groups. Association between epinephrine (P=0.003), vasopressin (P=0.018), and GII was observed. There was no difference between the total volume of enteral nutrition (TVEN) infused in the groups. However, the mean EN infused for the days when the patient was on PP was (70.0% ± 31.5) and for the days in supine position was (74.8% ± 27.3), P= 0.006. The PG had a longer time on MV (P=0.005) and

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ICU (P=0.003) and PP was associated with VAP (P=<0.001). The infused TVEN showed no association with VAP (P=0.09).
Conclusion: PP was a determining factor in GII and proved to be a risk factor for VAP, but the EN protocol seems to have ensured an adequate EN supply in PP and be a safe alternative.
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Introduction

SARS-CoV-2 pneumonia, known at the end of 2019, has variable clinical manifestations such as asymptomatic infection, hypoxemia, mild upper respiratory tract disease, severe viral pneumonia with respiratory failure, mechanical pulmonary impairment, multiple organ failure, and death [1,2]. About 6–10% of those infected require hospitalization, particularly in the Intensive Care Unit (ICU) [3,4] due to pulmonary involvement with a complication similar to acute respiratory distress syndrome (ARDS). Under these conditions, mechanical ventilation (MV) is one of the supports used and PP is an allied technique to promote the improvement of oxygenation and pulmonary recruitment [2].

Prone position (PP) is defined as a maneuver to rotate the patient from the supine position to the ventral decubitus, allowing for greater expansion of the dorsal regions of the lung [5]. Although PP is a frequent strategy in the treatment of patients infected with SARS-CoV-2, we still do not have protocols for the management of EN during the procedure. Although EN in PP is not contraindicated, data on EN administered in PP for critically ill patients are still scarce and of limited methodological quality, raising doubts about possible compromises related to EN tolerance, safety, and viability, as the increased intra-abdominal pressure may result in increased gastric residual volume (GRV), episodes of regurgitation or vomiting [6,7].

Current recommendations are for the early beginning of EN, use of the gastric position of the feeding catheter, use of gastrointestinal motility stimulators, and bed maintenance in reverse Trendelenburg [8,9].

In the current pandemic, the concern with the provision of nutritional needs has intensified, as patients have spent hours in PP and/or alternating between positions for many days during hospitalization [10]. This strategy can lead to significant energy and protein deficit, which is known to increase the number of complications, such as infections, time on MV, length of stay, and mortality [11–13].

The present study aimed to analyze the effectiveness and complications of EN, as well as clinical outcomes of critically ill patients diagnosed with COVID-19, in invasive MV and in PP.

Methodology

This is a prospective cohort study carried out at a Respiratory ICU from a tertiary hospital in Curitiba-Paraná, Brazil, approved by the Research Ethics Committee (nº 4,284,467).

Patients hospitalized between March 2020 and January 2021, aged $\geq$ 18 years, of both genders, diagnosed with COVID-19 and ARDS, undergoing invasive MV, who did or did not need the prone maneuver, were evaluated, being the sample for convenience. Exclusion criteria were patients not undergoing EN, post-surgical, pregnant and postpartum women, or those who did not have all the data recorded in their medical records.

The follow-up of patients in the study started from the moment of admission to the ICU until discharge to the ward or death. Data were collected from the patient's physical and electronic medical records, as well as nutritional monitoring forms. The Charlson Comorbidity Index (CCI) was used as the severity score [14].

Respiratory management

ARDS was classified by the responsible medical team according to Berlin definitions [15]. For this study, the most aberrant partial pressure value, oxygen to fraction of inspired oxygen (PaO2/FiO2), was collected within 24 hours after orotracheal intubation [16] or ICU admission of previously intubated patients.

PP was indicated and performed according to institutional protocol, following international criteria for PP in ARDS [5] and the envelope method. Cushions were used at the pelvis and thorax region, aiming to relieve abdominal pressure in the tibial region to ensure anatomical positioning of the feet and other cushions as needed for proper patient alignment.

The total length of stay in PP was defined by the multidisciplinary team, according to the patient's clinical response to the strategy, with the position being maintained for a minimum period of 16 hours, except in cases of severe hemodynamic instability.

Drug management

Sedation and use of neuromuscular blockers (NMB) were based on ICU protocols. The total volume administered for each drug was collected from the daily nursing report, which records this data every 2 hours. The dilution was calculated according to the ICU protocol and used in the statistical analysis the total amount of the drug and its exposure to the patient in 24 hours.

Enteral nutrition

EN was started as soon as possible, within 12–48 hours, via the nasogastric or orogastric route.

The composition of the EN was always prescribed by dietitians at the bedside, according to the protocol of the nutrition service in the pandemic. For obese and non-obese patients, the calculations usually aimed at an energy goal of 15–20 kcal/kg/day in the first week, progressing to 25kcal/kg/day according to the patient's clinical condition [9]. The goals were adjusted to 30kcal/kg/day, according to previous data for the rehabilitation phase [17], as long as there was no clinical contraindication. For patients with BMI <30 kg/m^2 the current/actual, reported, or estimated body weight (with anthropometric measurements [18] or by visual inspection of BMI [19]) was used to apply kcal/kg/day like mentioned above [9,17]. For BMI ≥30 kg/m^2 the ideal weight was considered [9]. Height was estimated through knee height [20]. Non-nutritional calories were considered (propofol -1.1 kcal/ml – and dextrose infusion – 3.4 kcal/gram), citrate was not used in renal replacement therapy [21].

Protein was gradually prescribed, aiming at the following goals: <0.8 g/kg/day, 1st and 2nd days; 0.8–1.2g/kg/day, 3rd to 5th day; and >1.2 g/kg/day from the 5th day [22], reaching up to 2.0 g/kg/day [9]. In the rehabilitation phase, the protein offer could reach 2.0–2.5 g/kg/day [17].

For obese patients, the following recommendation was considered: BMI between 30-40 kg/m^2 (2g/kg ideal weight) and BMI >40 kg/m^2 (2.5g/kg ideal weight), also prescribed gradually [9].

Enteral formulas (polymeric, oligomeric, with density ranging from 1.0 to 2.0 kcal/ml) were individually prescribed and availability was taken in account. These enteral formulas were administered by continuous infusion pump for 22h/day. Protein modules (whey-based and/or calcium caseinate diluted in water) were administered in fractions, at pre-established intervals, by the gravitational method, with or without interruption in the administration of enteral formulas. The speed was progressively determined based on the patient's tolerance.

GII records related to PP were: 1. Presence of GRV during PP; 2. Vomiting: return of a large volume of enteral formula through the oral cavity; 3. Diet regurgitation: enteral formula found in the oral or nasal cavity.

Constipation was considered “the absence of elimination of feces for 3 or more consecutive days” [23].

EN administration was recorded until its definitive suspension, and its adequacy was calculated daily and individually by the dietitian and presented as the volume of EN infused.

Outcome variables, including days on MV, days in the ICU, days of hospitalization, and mortality were collected from medical records. The incidence of VAP was obtained from the register of the hospital infection control committee.

EN protocol in PP

The protocol included training the nursing staff for: the administration of enteral formulas and protein modules; recording of total volume of infusion. Daily monitoring, recording of EN management and prokinetic administration were performed throughout the ICU stay. The protocol determined that in the supine position, the head of the bed was kept in decubitus at 30°. In PP, the bed was kept in reverse Trendelenburg at least at 10° [9].

The nutritional prescription was the same for the patient in the supine or prone position. A single modification performed was in the dilution volume of the protein modules in the PP (maximum of 100ml and 40% powder).

For the cases of patients already receiving EN before the prone maneuver, the following processes were followed:

1. Enteral diet was paused 1h before the maneuver and restarted 1h after positioning
2. There being no clinical contraindication, the same infusion speed that it had been receiving in the supine position was maintained, not exceeding 45ml/h

In case of occurrence of food regurgitation, vomiting or gastric stasis, EN was interrupted. The prokinetic prescription was revised, the catheter opened in a collection bottle and, according to the GRV, the following measures were taken if GRV>500ml in 6 hours EN was discontinued in case of VRG<500ml in 6 hours: EN was restarted at a lower infusion rate (23ml/h) until reassessment by the dietitian.

Statistical analysis

The patients were divided into 2 groups: prone group (PG), in which all members prone at some time during ICU stay, and supine group (SG), whose individuals remained in supine position throughout the hospitalization period.

All continuous variables were evaluated for normality. Variables that did not follow the normal distribution were analyzed using the Mann-Whitney U test. Other variables were analyzed using an independent sample t-test.

Data with non-normal distribution are presented as medians. No sample power analysis was performed due to the novelty of the disease during the observation period.

Analyzes were carried out using the “R” statistical program [24]. A two-tailed P <0.05 was considered statistically significant.

Univariate linear regression models were tested to verify the effect of each specific variable on the outcome. A multiple regression model was used to analyze which factors contributed to the GII, estimating the Odds Ratio and Confidence Intervals at 95%.

Generalized linear models were adjusted in the base package, while models with mixed effects were adjusted with the “lme 4” package [25].

To assess the effect of drugs on GII, a regression model of the quasipoisson class was used, with a logarithmic link function, due to overdispersion of the response variable. In the regression models mentioned above, the count of total complications at the individual level during the patient's hospital stay was considered.

Results

During the period, 609 patients were admitted and 121 were included in the study, 52 allocated in the PG and 69 in the SG.

Table 1
Characteristics of patients and clinical outcomes.

	Total n=121	Prone group n=52	Supine group n=69	P-value
Age (yrs)[a]	59,4±16,9	56,5 ±16,14)	61,0 ±17,5	0,142
Male sex n (%)	64 (52,9)	28 (54,7)	36 (52.2)	
CCI[b]	2 (0–7)	2 (1–3)	2 (1–4)	0,255
BMI (kg/m^2)[a]	30,1±7,6	32,1±8,2	28,4 ±6,9	0,031
PaO_2/FiO_2 ratio[b,c]	168 (58–420)	167 (58–284)	169,5 (62–420)	0,286
PaO_2/FiO_2 ratio <100 n (%)[c]	14 (13,0)	8 (7,40)	6 (5,55)	0,746
ICU LOS (days)[a]	15,5±10,8	18,7 ± 12,2	12,9 ± 8,9	0,003
MVT (days)[a]	12,8±8,6	15,5 ± 9,8	11,0 ± 7,4	0,005
Hospital LOS (days)[a]	22,5±15,8	22,7 ± 14,9	22,6 ± 16,6	0,955
VAP n (%)	12 (9,9)	9 (75)	3 (25)	<0,001
Mortality n (%)	83 (68,6)	34 (41)	49 (59)	0,452

Abbreviations: CCI, Charlson Comorbidity Index; BMI, body mass index; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; LOS, length of stay; MVT, mechanical ventilation time; VAP, ventilator-associated pneumonia.
Significant results (P<0,05).
[a] Mean±SD.
[b] Median (interquartile range).
[c] n=108.

The data of 1990 days were evaluated from all de patients (mean of 15.5 days of hospitalization – minimum 2 days, maximum 57 days), of these, 192 days the patients were in PP, with a mean time in PP of 25 hours and 27 minutes (±0.46) (Table 1).

Considering the CCI, 71.90% were classified with scores 1 or 2. When analyzing the effect of the CCI on complications, adjusting for the prone effect, there was no significance (P= 0.484; OR =1.12; 95% CI 0.81–1.54).

From all the patients 89 (73.5%) did not have GII. PG had 30.8% of GII, and SG, 23.2% (P=0.805). 16 of the PG had GII, 9 of them had 1 episode of complication, 3 had 2 complications, 3 had 3 complications and another had 1. In the SG, 16 had GII, 7 of them had only 1 episode of complication, 4 patients had 2 complications, 3 had 3 episodes, 1 had 4 and a single developed 12 GII.

From the PG, prokinetics were not prescribed in 22.4% of days and for SG, 22% of days (P=0.148).

Comparing the density of the enteral formulation received between PG and SG for 1.2 kcal/ml: 26.2% vs 30.4% of days; 1.5 kcal/ml: 47.5% vs 49.3% and 2 kcal/ml: 10.3% vs 6.9% of days. The only difference between groups was 2.0kcal/ml formulation (P=0.014).

The mean EN infusion rate was 43.9 (±16.0) ml/h and 43.1 (±16.2) ml/h for PG and SG (P=0.740), respectively.

Considering the infused EN volume (mean of the prescribed EN volume versus mean of the infused EN volume during ICU length of stay), PG mean was 76,2% (±27.6), while in SG was 74.5% (±27.5), P=0.939.

During hospitalization, 12 patients were diagnosed with VAP (Table 1), 9 (75%) were from the PG and of these 9, 6 (66.7%) had the diagnosis made after some episode of prone. An association of prone positioning with VAP was observed (P=<0.001; OR=4.10; 95%CI 2.89–5.82). When assessing whether the adequacy of the EN volume infused would have an effect on VAP, no significance was found (P=0.09).

PG had a longer time in the mechanical ventilator (P=0.005) and stay in the ICU (P=0.003). The length of hospital stays and mortality did not show significant differences between the groups (Table 1).

Analysis of drug exposure and GII considering the total population regardless of bed position

The effect of 17 drugs was evaluated considering the number of GII: norepinephrine, epinephrine, vasopressin, dobutamine, nitroglycerin, fentanyl, remifenta, midazolam, ketamine, clonidine, propofol, dexmedetomidine, atracurium, cisatracurium, rocuronium, vecuronium, amiodarone, and nitroprusside. Larger amounts in total dose exposure to the vasoactive drugs (VAD) epinephrine – 26.3 mg/24h (minimum 13.1 mg/24h, maximum 30.9 mg/24h)- (P=0.003) and vasopressin – 20.5 mg/24h

(minimum 3.6 mg/24h, maximum 23.8 mg/24h) - (P=0.018) were associated with a higher number of GI. This was due to an outlier patient (12 GII records and exposed to significant larger amounts of these drugs). Therefore, when the outlier patient was excluded, there was a change in the effect of the drugs on the GII, thus the association with the NMBs atracurium (P=0.006) and vecuronium (P=0.043) was evidenced.

Daily evaluation of the period in the supine position and PP

The presence of GII was associated with PP (P=0.000; OR=3.91; 95%CI 1.84–8.30).

When each GII was considered separately (per day of EN) vomiting and diet regurgitation in oral cavity had no relationship with PP (P=0.640; P=0.890, respectively), unlike gastric stasis, which had a significant effect (P=0.0007; OR= 4.36; 95%CI 1.86–10.21).

The mean EN infused for the days when the patient was on PP was (70.0% ± 31.5) and for the days in supine position was (74.8% ± 27.3), P= 0.006.

Analysis of confounding factors that could contribute to GIIs considering the effect of PP

In the univariate analysis of possible factors (considered by the team) that could contribute to GII, given the effect of prone: VADs (noradrenaline, epinephrine, vasopressin), prokinetic administration, protein modules in a gravitational method, enteral nutrition infusion rate ≥45ml/h, enteral formulation (2,0 kcal/ml), age, BMI, constipation, PP time >24 hours, and having diabetes mellitus diagnosis, no significant effect was found (Table 2). In this test, it is highlighted that the presence of GII is evaluated and not the number of occurrences.

When the outlier patient is again removed from the analysis, no data changes, and the NMBs atracurium (P=0.088; OR=1.00; 95%CI 0.1–1.00) and vecuronium (P=0.999; OR=1, 53; 95%CI 0 - ∞), also had no effect on the GII.

As for the gravitational administration of protein module, 8 patients received calcium caseinate-based protein for a mean of 3.1 days (minimum 1 day, maximum 6 days). Among the 8 patients, 4 individuals were part of the PG, but no calcium caseinate-based module was administered during PP. Only whey-based protein modules were administered in PP.

Patients presented 38.1% of the days evaluated with constipation.

Analysis of the joint effect of confounding factors on GII

The joint effect of the confounding variables on the GII is shown in table 3. Logistic regression detected PP, noradrenaline, and constipation as significant factors to explain the occurrence of GII regardless of the patient's position. From the model adjustment, progressively removing each less

Table 2
Univariate regression of possible factors (considered by the team) contributing to the GII, given the prone effect.

Factors contributing to GII	P-value	OR (CI 95%)
Noradrenaline	0,058	1,01 (1,00–1,03)
Epinephrine	0,405	1,01 (0,98–1,04)
Vasopressin	0,812	1,00 (0,97–1,02)
Prone	0,000	3.91 (1,84–8,31)
Constipation	0,375	0.76 (0,42–1,38)
Prokinetic	0,162	1,77 (0,80–3,93)
BMI	0,183	1,05 (0,98–1,13)
Infusion speed ≥45ml/h	0,630	1,15 (0,65–2,05)
Enteral formulation (2,0 kcal/ml)	0,516	0,69 (0,23–2,11)
Use of protein module (gravitational)	0,300	1,38 (0,75–2,52)
Prone time >24 hours	0,828	1,17 (0,27–5,02)
Diabetes mellitus	0,886	1,10 (0,28–4,32)
Age	0,751	1,00 (0,98–1,03)

Abbreviations: BMI, body mass index; GII, gastrointestinal intolerance; OR, odds ratio. Significant results (P<0.05).

Table 3
Multivariate regression of possible factors contributing to GII.

Factors contributing to GII	*P*-value	(CI 95%)
Noradrenaline	0,012	(0,005; 0,042)
Prone	0,002	(0,578; 2,707)
Constipation	0,046	(-1,741; -0,014)
Prokinetic	0,500	(-0,623; 1,290)
BMI	0,062	(-0,172; 0,004)
Infusion speed ≥45ml/h	0,319	(-0,485; 1,489)
Enteral formulation (2,0 kcal/ml)	0,174	(-3,630; 0,656)
Use of protein module (gravitational)	0,222	(-1,461; 0,340)
Prone time >24 hours	0,625	(-1,417; 2,358)
Diabetes mellitus	0,190	(-4,318; 0,860)
Age	0,476	(-0,052; 0,024)

Abbreviations: BMI, body mass index; GII, gastrointestinal intolerance; CI: 95% confidence interval. Significant results ($P<0.05$).

significant variable, only noradrenaline remained ($P=0.058$; 95%CI -0.00 - 0.026) and PP ($P=0.000$; 95% CI 0.549–2.072), this being the only one variable independently associated with GII.

With the exclusion of the outlier patient, it is found an association between GII and BMI ($P=0.046$), PP ($P=0.000$) and constipation ($P=0.027$); and by adjusting the model, the only variables independently associated are PP ($P=0.000$) and infusion rate ≥45ml/h ($P=0.041$).

Discussion

PP proved to be a risk factor for GII, however, it is favorably observed that the adoption of the properly trained team protocol and the participation of the dietitian in bedside care seems to have ensured an adequate EN supply during ICU stay, regardless of PP or supine.

Among the various mechanisms that can change gastrointestinal function and dietary tolerance in critically ill patients (inflammatory disease process, myoelectric and neuroendocrine processes, in addition to various clinical conditions and treatment approaches) [26–28] are VADs, whose concern regarding the use and dose is due to possible mesenteric ischemia and non-occlusive intestinal necrosis [29]. In this study, we found an association of adrenaline and vasopressin with GII.

Several researchers have shown that vasopressin or epinephrine administration leads to enteric and gastric hypoperfusion, impairs splanchnic blood flow, with consequent lower local oxygen consumption, higher lactate, and damage to the intestinal mucosa [30,31]. Signs of intolerance such as increased GRV, nausea, emesis, and abdominal distension may appear [32]. This factor explains the analyzes when including the outlier patient exposed to epinephrine and vasopressin, and who had the highest number of GII. However, when this outlier patient is removed from the analysis, vasopressors did not present an association, unlike NMBs (vecuronium and atracurium) do. Knowing that NMBs do not have a paralyzing effect on the intestinal smooth muscles, seems that EN intolerance happens because of the concomitant use of narcotics, which reduce the rate of gastric emptying [33] and for intubated COVID-19 patients required substantially higher doses of narcotics, sedatives to maintain adequate sedation and ventilation [34].

It is known that NMB relaxes the skeletal muscle and does not act on smooth muscle, therefore, other underlying factors (prolonged immobility, opiates, fluid overload) could be associated with the GII found [32,35,36]. This would explain our finding since in the univariate analysis, vecuronium, and atracurium did not interfere in the result.

It is worth emphasizing that, usually, in the treatment of ARDS, NMBs have been used for a short period [36], and extreme amounts of exposure to the drug for a long time, as performed in the management of severe COVID-19 [37], have not yet been studied. Furthermore, alterations in upper esophageal sphincter tone have been reported with the use of vecuronium and atracurium, which means a higher risk of aspiration due to reduced tone and difficulty in swallowing [38,39]. Therefore the effect of NMBs on the gastrointestinal tract in critically ill patients remains unclear, always being

necessary the gastrointestinal tolerance individual evaluation in patients exposed to excessive amounts for a prolonged time.

Despite all these factors, unlike the high frequency of complications found by Montejo JC, our study showed a lower occurrence of GII (27.05%) [35], similar to the study by Osuna-Padilla *et al.* with COVID-19 patients (35%), however, unlike this work, they evaluated only 7 days of hospitalization [40].

In this study, EN in PP presented results consistent with the study by Reignier *et al.* (2004), who showed a higher risk of GII, mainly associated with gastric stasis [41]. At the unit where this protocol was developed, GRV is not routinely performed, as randomized clinical trials have shown that it does not correlate with a higher incidence of aspiration and pneumonia [42].

In the present study, were used PG similar strategies to those proposed by Reignier *et al.* (2010): elevated head of the bed (reverse Trendelenburg at 25°) and prophylactic prokinetic agent (erythromycin) [43]. However, there was failure to prescribe prokinetics agents (bromopride) in 28.7% of the days evaluated in the PG. The differential of the present work is the daily assessment of the effect of PP on GII throughout the ICU stay. The analysis of the effects of PP in patients with COVID-19 is still scarce, however, in other critical patients, PP does not seem to increase the intolerance or complications of EN [36].

EN intolerance may result in inadequate energy-protein supply and consequent adverse effects. Regarding nutrient supply, when evaluated daily, PP has a strong impact on EN supply. Comparing between PG and SG, this statistical difference is not found, which we can associate with a possible compensation over the days of EN, demonstrating the adequacy of the suggested protocol, since daily monitoring by dietitians intensifies and adjusts the dietary prescription improving nutritional support, as demonstrated in a previous study [44]. Wischmeyer *et al.* (2021) reports that the amount of EN infused, before the pandemic in the ICU, corresponds to <50% of the prescribed goal [32]. In this scenario, PP is often not a reason for therapy interruption, therefore, we can say that the present study was able to offer a significant amount of EN, in agreement with the results found by Saez de la Fuente *et al.* [45].

Even though it is not part of the protocol's methodology, the infusion speed ≥45ml/h occurred in PP in some moments in clinical practice due to patient's needs and in common agreement with the multidisciplinary team.

Regarding the high prevalence of constipation observed, the drug regimen and even hypoxemia may explain the finding [46]. This complication was also found by Osuna-Padilla *et al.* in about 87% of COVID-19 patients [40]. The impact of constipation in critically ill patients has been previously related to food intolerance, abdominal distension, vomiting, difficulties in weaning from MV, and pneumonia due to aspiration of gastric contents [47].

High BMI and infusion speed would be associated with a possible increase in intra-abdominal pressure caused by PP plus excessive abdominal magnitude or PP plus abdominal distension due to increase EN volume, respectively. Ni L *et al.* (2018) found a positive correlation between intra-abdominal pressure and the patient's BMI in PP, ranging from 9 to 15 mmHg, even with the upper chest and pelvis suspended [48]. In our study, we also used the strategy with cushions at the pelvis and thorax region. Reignier J *et al.* (2010) reached a maximum infusion rate of 85 ml/h and administered erythromycin (250 mg intravenously every 6 hours) for all patients on PP, which did not provide an increase in GII or VAP [43].

In our study, PP was associated with the development of VAP, different from previous evidence where PP plays a role in preventing this condition [49]. In addition to interfering with the achievement of nutritional goals, intolerance can lead to aspiration and pneumonia, especially in mechanically ventilated ICU patients [35,50].

However, the relationship between intolerance or high GRV and aspiration is still questionable [51]. Even so, when the influence of EN infusion on the occurrence of VAP was evaluated, patients who showed greater adequacy in the provision of EN had no association with the development of VAP.

PG patients had a longer stay on MV and in the ICU. Considering that these outcomes were substantially higher than in ARDS in non-COVID-19 patients [52], the most unfavorable events among COVID-19 patients in PP can be explained by the severity of the disease. Further controlled studies are needed. However, based on these data and on the literature, it is appropriate to state that PP has a profound influence on GII in critically ill patients with COVID-19 on MV.

The inadequacy in some records of the EN volume administered (excluded data), which is not under our control, may have hampered the evaluation of our results. Another limitation is the small sample size for the prospective design, considering the 609 hospitalizations in the analyzed period, however the study was carried out by frontline professionals at a time of high work demand during the pandemic.

We attribute this promising supply of EN to frequent bedside monitoring by dietitians and staff, responsible for controlling complications and avoiding undue suspension or delays of EN, as well as respecting the individualization of therapy. Favoring the use of EN in PP, the need for prophylactic measures and rigorous monitoring of tolerance to therapy is emphasized.

Conclusion

The EN management protocol in PP used in this study (following prophylactic measures and rigorous monitoring of EN tolerance) seems to have ensured an adequate EN supply during ICU stay, and be a safe alternative to maintain quality EN in critically ill patients with COVID-19 under MV. Thus sharing this experience could help other centers in the effectiveness of EN in PP.

In addition, PP proved to be a risk factor for VAP but was not aggravated using EN according to the protocol used in this study.

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Author contributions

J.A de Paula: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Investigation, Formal analysis, Visualization, Data Curation, Project administration, Supervision. **E. I. Rabito:** Formal analysis, Data Curation, Project administration, Supervision, Writing - Review & Editing. **S.R Justino:** Methodology, Formal analysis, Writing - Review & Editing, Project administration, Supervision. **L.S Leite:** Investigation, Writing - Review & Editing, Project administration, Supervision. **D. Dantas:** Investigation, Data Curation. **J. S. M da Silva:** Investigation, Data Curation. **L. F Maffini:** Investigation, Data Curation. **O. R Junior**: Project administration, Supervision, Writing - Original Draft, Writing - Review & Editing.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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