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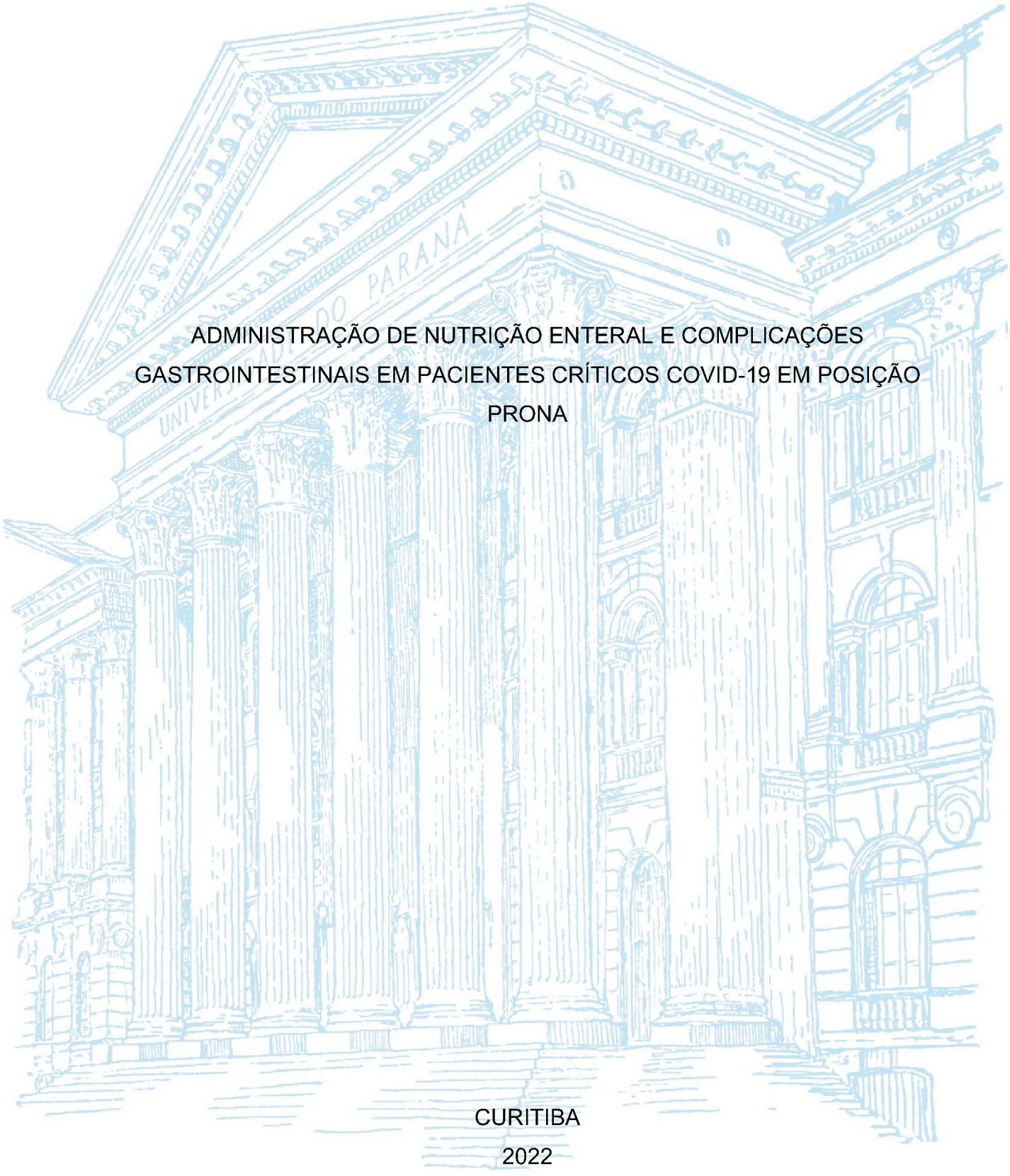

ADMINISTRAÇÃO DE NUTRIÇÃO ENTERAL E COMPLICAÇÕES GASTROINTESTINAIS EM PACIENTES CRÍTICOS COVID-19 EM POSIÇÃO PRONA

CURITIBA

2022

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Dissertação apresentada ao curso de Pós-Graduação em Medicina Interna e Ciências da Saúde, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Medicina Interna.

Orientador: Prof. Dr. Odery Ramos Junior

Coorientadora: Profa. Dra. Estela Iraci Rabito

CURITIBA

2022

P324 Paula, Jéssica Alves de
Administração de nutrição enteral e complicações gastro-intestinais em pacientes críticos covid-19 em posição prona [recurso eletrônico] / Jéssica Alves de Paula. – Curitiba, 2022.

Dissertação (Mestrado) – Programa de Pós-Graduação em Medicina Interna e Ciências da Saúde. Setor de Ciências da Saúde. Universidade Federal do Paraná.
Orientador: Prof. Dr. Odery Ramos Junior
Coorientadora: Profa. Dra. Estela Iraci Rabito

1. Covid-19. 2. Decúbito ventral. 3. Nutrição enteral. I. Ramos Junior, Odery. II. Rabito, Estela Iraci. III. Programa de Pós-Graduação em Medicina Interna e Ciências da Saúde. Setor de Ciências da Saúde. Universidade Federal do Paraná. IV. Título.

NLM: WB 410

FICHA CATALOGRÁFICA ELABORADA PELO SISTEMA DE BIBLIOTECAS/UFPR
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PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO MEDICINA INTERNA E CIÊNCIAS DA SAÚDE - 40001016012P1

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação MEDICINA INTERNA E CIÊNCIAS DA SAÚDE da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **JÉSSICA ALVES DE PAULA** intitulada: **"ADMINISTRAÇÃO DE NUTRIÇÃO ENTERAL E COMPLICAÇÕES GASTROINTESTINAIS EM PACIENTES CRÍTICOS COVID-19 EM POSIÇÃO PRONA."**, sob orientação do Prof. Dr. ODERY RAMOS JUNIOR, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de mestra está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

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Dedico este trabalho à todas as famílias que perderam seus entes queridos para a COVID-19 neste terrível momento que vivemos da pandemia.

AGRADECIMENTOS

Aos meus pais, Aguinaldo Castelo de Paula e Márcia Cristina Alves Castelo, por sempre apoiarem os meus sonhos e os meus estudos.

À minha irmã Mirella Alves de Paula, professora espetacular, a qual sempre me incentiva, mesmo a tantos quilômetros de distância.

Ao meu esposo Erik da Silva Guimarães, que sempre esteve ao meu lado e ao meu filho, que veio ao final do curso me dar forças para seguir batalhando. Sou extremamente grata pelo que conquistamos e pela felicidade que me proporcionam.

Este trabalho só foi possível graças ao voto de confiança da Professora Dra. Estela Iraci Rabito e do Professor Dr. Odery Ramos Júnior, que acreditaram no meu desempenho e contribuíram para meu crescimento acadêmico e profissional.

À colega e profissional maravilhosa Dra. Sandra Justino, por ter sido um dos meus maiores exemplos na carreira, por ter me ensinado tanto e ter sido um especial ombro amigo no momento mais difícil da pandemia.

À colega e parceira Luiza Leite, por caminhar junto comigo e auxiliar em todos os momentos profissionais e pessoais.

Às nutricionistas Danielle Dantas, Jéssica Sayume, Larissa Maffini, Gabriela Lazzaron, por terem contribuído com o projeto desde início.

Ao Complexo Hospital de Clínicas da Universidade Federal do Paraná, minha segunda casa, a qual defendo sempre orgulhosamente por desde a graduação ter me transformado na profissional que sou hoje.

Por último, a todos os profissionais de diferentes áreas que permaneceram na linha de frente contra a COVID-19. Que a pandemia possa nos ajudar a ressignificar a nossa existência na busca de um mundo melhor.

E minha solidariedade às famílias que perderam seus entes queridos.

RESUMO

Introdução: A posição prona, utilizada no tratamento dos pacientes críticos infectados com SARS-CoV-2, pode ser uma barreira para o fornecimento das necessidades nutricionais, sendo que ainda não dispomos de protocolos do manejo da Terapia Nutricional Enteral durante o procedimento. O objetivo do estudo foi analisar a efetividade e complicações da Terapia Nutricional Enteral em posição prona, assim como desfechos clínicos. **Metodologia:** Estudo de coorte prospectivo com pacientes em Terapia Nutricional Enteral e com *coronavirus disease 2019* (COVID-19), em ventilação mecânica, que necessitaram ou não da posição prona. Intolerâncias gastrointestinais relacionadas à posição prona foram avaliadas e correlacionadas com possíveis fatores de confusão. O efeito das medicações sob estas intercorrências também foi analisado. Além disso, estudou-se o volume infundido das fórmulas enterais, dias em ventilação mecânica, tempo na Unidade de Terapia Intensiva (UTI), de internação hospitalar, pneumonia associada à ventilação mecânica (PAV) e mortalidade. As informações foram coletadas do prontuário físico e eletrônico do paciente, além das fichas de avaliação e acompanhamento nutricional. Os dados foram avaliados diariamente comparando a posição prona e supina. Também foi realizada a comparação entre o grupo prona (GP) e grupo supina (GS). **Resultados:** Foram incluídos 121 pacientes, sendo 52 do GP e 69 do GS. No total foram avaliados 1990 dias de internamento. Manifestações de intolerâncias gastrointestinais como vômitos, regurgitação e estase estiveram presentes em 32 pacientes (26,44%). O GP apresentou 30,2% de intolerâncias gastrointestinais, e o GS, 23,2%, sem diferença entre ambos (p=0,805). A posição prona foi associada às intolerâncias gastrointestinais (p=0,000). Foi observada associação entre epinefrina (p=0,003), vasopressina (p=0,018) e intolerâncias gastrointestinais. Não houve diferença entre o volume total de nutrição enteral infundido entre os grupos. No entanto, a média de nutrição enteral infundida para os dias em que o paciente estava em posição prona foi (70,0% ± 31,5) e para os dias em posição supina foi (74,8% ±27,3), p=0,006. O GP apresentou tempo maior na ventilação mecânica (p=0,005) e UTI (p=0,003) e posição prona associou-se à PAV (p= <0,001). O volume total de nutrição enteral infundido não mostrou associação com PAV (p=0,09). **Conclusão:** A posição prona foi um fator determinante das intolerâncias gastrointestinais e mostrou-se fator de risco para PAV, porém o protocolo de Terapia Nutricional Enteral parece ter garantido uma oferta adequada de nutrição enteral em posição prona e ser uma alternativa segura.

Palavras-chave: COVID-19; posição prona; nutrição enteral.

ABSTRACT

Background: The prone position used in the treatment of critically ill patients infected with SARS-CoV-2, may be a barrier to the provision of nutritional needs, and we still do not have protocols for the management of Enteral Nutrition Therapy during the procedure. This study aimed to analyze the effectiveness and complications of Enteral Nutrition Therapy in the prone position, as well as clinical outcomes. **Methods**: Prospective cohort study with patients in Enteral Nutrition Therapy and coronavirus disease 2019 (COVID-19), on mechanical ventilation, which whom needed or not prone position. Gastrointestinal intolerances related to prone position were evaluated and correlated with possible confounding factors. The effect of medications on these complications was also analyzed. Furthermore, it was studied the infused volume of enteral formulas, days on mechanical ventilation, Intensive Care Unit (ICU) length of stay, hospital length of stay, ventilator-associated pneumonia (VAP) and mortality. Information was collected from the patient's physical and electronic medical records, in addition to nutritional assessment and monitoring forms. The data were evaluated daily comparing prone and supine positions. A comparison was also made between the prone group (PG) and supine group (SG). **Results**: 121 patients were included, 52 from the PG and 69 from the SG. In total, 1990 days of hospitalization were evaluated. Manifestations of gastrointestinal intolerances such as vomiting, regurgitation and stasis were present in 32 patients (26.44%). The PG presented 30.2% of gastrointestinal intolerances, and the SG, 23.2%, with no difference among groups (p=0,805). The prone position was associated with gastrointestinal intolerance (p=0,000). Association between epinephrine (p=0,003), vasopressin (p=0,018), and gastrointestinal intolerances was observed. There was no difference between the total volume of enteral nutrition infused in the groups. However, the mean of enteral nutrition infused for the days when the patient was on prone position 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 mechanical ventilation (p=0,005) and ICU (p=0,003), and prone position was associated with VAP (p=<0,001). The total volume of enteral nutrition infused was not associated with VAP (p=0,09). **Conclusion**: Prone position was a determining factor in gastrointestinal intolerances and proved to be a risk factor for VAP, but the Enteral Nutrition Therapy protocol seems to have ensured an adequate enteral nutrition supply in prone position and be a safe alternative.

Keyword: COVID-19; prone position; enteral nutrition.

LISTA DE ABREVIATURAS OU SIGLAS

BNM	- Bloqueador neuromuscular
GP	- Grupo prona
GS	- Grupo supina
ICC	- Índice de Comorbidade de Charlson
IGIs	- Intercorrências gastrointestinais
IMC	- Índice de massa corporal
NE	- Nutrição enteral
PAV	- Pneumonia associada à ventilação mecânica
PP	- Posição prona
SDRA	- Síndrome do desconforto respiratório agudo
TNE	- Terapia Nutricional Enteral
UTI	- Unidade de Terapia Intensiva
VRG	- Volume residual gástrico
VM	- Ventilação mecânica

SUMÁRIO

1 INTRODUÇÃO

A pneumonia por SARS-CoV-2, conhecida no final de 2019, possui manifestações clínicas variáveis como infecção assintomática, hipoxemia, doença leve do trato respiratório superior, pneumonia viral grave com insuficiência respiratória, comprometimento mecânico pulmonar, falência de múltiplos órgãos e morte (CHINESE CENTER FOR DISEASE CONTROL AND PREVENTION, 2020; ZHOU *et al.,* 2020). Cerca de 6 a 10% dos infectados têm necessidade de hospitalização, em particular em Unidade de Terapia Intensiva (UTI) (WANG *et al.*; WHO, 2020) devido ao acometimento pulmonar com complicação semelhante à síndrome do desconforto respiratório agudo (SDRA). Nestas condições a ventilação mecânica (VM) é um dos suportes empregados e a posição prona (PP) uma técnica aliada para promover a melhora da oxigenação e recrutamento pulmonar (ZHOU *et al.,* 2020).

A PP é definida como uma manobra de rotação do paciente da posição supina para decúbito ventral, possibilitando uma maior expansão das regiões dorsais do pulmão (GUÉRIN *et al.,* 2013). Apesar da PP ser uma estratégia frequente no tratamento dos pacientes infectados com SARS-CoV-2, ainda não dispomos de protocolos do manejo da Terapia Nutricional Enteral (TNE) durante o procedimento. Embora a nutrição enteral (NE) na PP não seja contraindicada, ainda são escassos e de qualidade metodológica limitada os dados sobre NE administrada na PP para pacientes críticos, gerando dúvidas sobre os possíveis comprometimentos relacionados a tolerância, segurança e viabilidade da NE, pois o aumento da pressão intra-abdominal pode resultar em volume residual gástrico (VRG) elevado, episódios de regurgitação ou vômitos (MACHADO, RIZZI, SILVA, 2020; BRUNI *et al.,* 2020).

As recomendações atuais são de início precoce da TNE, uso da posição gástrica do cateter de alimentação, uso de agentes estimuladores da motilidade gastrointestinal e manutenção da cama em *Trendelenburg* reverso (BARAZZONI *et al.,* 2020; MARTINDALE *et al.,* 2020).

1.1 JUSTIFICATIVA

Na pandemia da COVID-19, que iniciou em 2020, intensificou-se a preocupação com o fornecimento das necessidades nutricionais, visto que os

pacientes em cuidados intensivos permaneceram horas em PP e/ou alternando entre as posições por muitos dias durante o internamento (BERRILL, 2021). Esta estratégia de posicionamento pode acarretar significativo déficit energético e proteico, que sabidamente aumenta o número de complicações, tais como infecções, tempo em VM, tempo de internação e mortalidade (SINGER *et al.*, 2019; REINTAM *et al.*, 2017; VILLET *et al.*, 2005).

Devido à falta de conhecimentos na comunidade científica, a assistência nutricional de pacientes em cuidados intensivos diagnosticados com a doença do coronavírus 2019 (COVID-19), é orientada para ser realizada de acordo com as diretrizes destinadas a pacientes críticos em geral, com comprometimento pulmonar (MARTINDALE *et al.,* 2020).

O estudo visa a contribuir com a demonstração de dados após a aplicação de um protocolo específico de TNE na PP em pacientes críticos diagnosticados com COVID-19 em VM invasiva. A partir do conhecimento da efetividade e desafios da TNE neste cenário clínico, torna-se possível obter uma melhor compreensão da NE do paciente com necessidade de posicionamento prona, contribuindo com o avanço e, até mesmo uma nova abordagem, na assistência nutricional desses pacientes.

1.2 OBJETIVO

1.2.1 Objetivo geral

O presente estudo objetivou analisar a efetividade e complicações da TNE, assim como desfechos clínicos de pacientes críticos diagnosticados com COVID-19, em VM invasiva e em PP.

1.2. 2 Objetivos específicos

Os objetivos específicos do trabalho são:

a) Avaliar as diferenças entre o grupo prona (GP) e grupo supina (GS);
b) Avaliar as intercorrências gastrointestinais (IGIs) relacionadas à PP e comparar a ocorrência na PP e posição supina;
c) Avaliar a associação da PP com a presença de IGIs;

d) Avaliar os possíveis fatores de confusão que podem contribuir para as IGIs, considerando o efeito da PP;
e) Avaliar o efeito dos medicamentos sob as IGIs;
f) Avaliar a incidência de pneumonia associada à ventilação mecânica (PAV), sua relação com a PP e com o volume total de NE infundido;
g) Avaliar as variáveis de desfecho: dias em VM, dias na UTI, dias de hospitalização, mortalidade, e comparar entre o GP e GS.

2 REVISÃO DE LITERATURA

2.1 PANDEMIA DA COVID-19

No início de dezembro de 2019, os primeiros casos de pneumonia de origem desconhecida foram identificados em Wuhan, na China. O patógeno denominado como síndrome respiratória aguda grave do coronavírus 2 (SARS-CoV-2) é o responsável pela COVID-19, a qual se espalhou rapidamente, tornando-se uma emergência em saúde pública, com alta taxa de mortalidade e classificada como pandemia pela Organização Mundial da Saúde em março de 2020 (GUAN *et al.*, 2020).

Aproximadamente 15% dos casos desenvolvem doença grave caracterizada por dispneia, hipóxia e alterações pulmonares; 5% requerem internação UTI devido a insuficiência respiratória por SDRA, choque séptico, acidose metabólica, disfunção da coagulação e de múltiplos órgãos (RAHMAN *et al.,* 2021).

Entre os pacientes na UTI com COVID-19, 29,1% a 89,9% necessitam de VM invasiva (WANG, 2020; RICHARDSON, 2020). Dados de pacientes internados com COVID-19 durante os primeiros 5 meses da pandemia no Brasil mostraram que 39% dos pacientes foram admitidos na UTI, sendo que 23% necessitaram de VM invasiva (RANZANI *et al.*, 2021).

2.2 SÍNDROME DO DESCONFORTO RESPIRATÓRIO AGUDO E A POSIÇÃO PRONA

As características da insuficiência respiratória relacionada à COVID-19 atendem à definição de SDRA. Caracterizada como uma síndrome complexa e heterogênea causada por múltiplas etiologias, a SDRA está relacionada à resposta inflamatória exacerbada mediada por citocinas, que causa lesão pulmonar grave e de órgãos sistêmicos (LENTZ *et al.*, 2020).

A SDRA é um diagnóstico clínico que se baseia nos critérios de Berlim (RANIERI *et al.*, 2012) e sua característica histológica é o dano alveolar difuso, também observado em casos de autópsia de pacientes com COVID-19 (LENTZ *et al.*, 2020).

Uma vez diagnosticada a SDRA, o tratamento se concentra na manutenção da oxigenação e na prevenção da lesão pulmonar induzida pelo ventilador através da ventilação protetora pulmonar (LENTZ *et al.*, 2020).

Uma estratégia terapêutica que se destaca é a PP, utilizada desde 1970 para melhorar a oxigenação e os resultados na SDRA (PIEHL, BROWN, 1976; DOUGLAS, 1977). Consiste em posicionar o paciente em decúbito ventral, o que resulta em distribuição mais uniforme da aeração, melhora da relação ventilação/perfusão, da mecânica pulmonar e da parede torácica, além de aumento da depuração de secreções (KOULOURAS et al., 2016; GUÉRIN *et al.,* 2013*;* GATTINONI *et al.,* 2001).

A PP tem sido demonstrada em vários estudos como protetora da lesão pulmonar induzida pelo ventilador, contribuindo na redução da duração da VM e na taxa de mortalidade (GUÉRIN *et al.,* 2013; LENTZ *et al.*, 2020).

O posicionamento prona deve ser considerado em pacientes que apresentem alteração grave de troca gasosa, caracterizada por uma relação de pressão parcial de oxigênio arterial (PaO_2) e fração inspirada de oxigênio (FiO_2) inferior a 150 mmHg, sendo mais benéfico permanecer na posição por pelo menos 12 a 16 horas (ALHAZZANI *et al.*, 2020).

2.3 TERAPIA NUTRICIONAL ENTERAL E POSIÇÃO PRONA

2.3.1 Importância da Nutrição Enteral

Em pacientes graves, a NE é a via preferencial e a literatura científica, assim como, as principais diretrizes de nutrição na UTI enfatizam que a NE preserva a

integridade da mucosa do trato gastrointestinal, previne a translocação bacteriana, atenua a resposta inflamatória de fase aguda mediada por citocinas, diminui complicações infecciosas, tempo de permanência na UTI, bem como custos hospitalares (MCCLAVE *et al.,* 2016; SINGER *et al.*, 2019; REINTAM *et al.*, 2017, HEYLAND, D.K. *et al.* 2003).

O fornecimento adequado de macro e micronutrientes a pacientes críticos é essencial para o funcionamento ideal das células e órgãos, para a cicatrização de feridas (CASAER e ZIEGLER, 2015), estando o acúmulo de déficit energético e proteico associado a resultados adversos em vários estudos (SINGER *et al.*, 2019; REINTAM *et al.*, 2017; VILLET *et al.*, 2005). Além disso, a perda muscular esquelética relacionada à UTI parece ser um fator importante na morbidade dos sobreviventes da doença crítica prolongada (CASAER e ZIEGLER, 2015). Segundo Wischmeyer e San-Millan (2015): "sem dúvida, a preservação e recuperação da massa corporal magra, assim como, da função muscular após uma doença crítica não podem ser alcançadas sem o fornecimento adequado de calorias e proteínas".

A NE deve ser considerada uma parte crítica dos esforços iniciais de assistência, após as medidas de ressuscitação, porém, a desnutrição iatrogênica e a subalimentação são práticas onipresentes nas UTIs em todo o mundo (WISCHMEYER, 2021), chegando ao fornecimento menor que 50% da meta prescrita, mesmo em pacientes desnutridos (CAHILL *et al.*, 2010) seja por questões de tolerabilidade, à gravidade do paciente crítico, ou mesmo devido à propagação de mitos no fornecimento precoce da NE na UTI (MCCLAVE *et al.*, 2016; PEEV *et al.*, 2015; WISCHMEYER, 2021).

2.3.2 Desafios da Nutrição Enteral na Posição Prona

Considerando o exposto acima, intensificou-se a preocupação com o fornecimento das necessidades nutricionais dos pacientes críticos com COVID-19, visto que eles permanecem horas em PP e/ou alternando entre as posições por muitos dias durante o internamento na UTI (BERRILL, 2021). E há apreensão para alimentar pacientes em decúbito ventral devido ao aumento da pressão intra-abdominal, concomitante ao tratamento comum com uso de agentes sedativos e bloqueadores neuromusculares em altas doses, além dos agentes vasoativos, adicionando possíveis barreiras na tolerância à NE. Esse cenário leva a maior risco de êmese,

VRG elevado, e aspiração do conteúdo gástrico (Ni *et al*., 2018; BEHRENS *et al.,* 2021).

Os inúmeros questionamentos quanto ao manejo da TNE levaram as diretrizes a estimular a NE precoce em pacientes em PP, mas sem especificar quantidade, progressão e efeitos adversos do procedimento, levando às Instituições a desenvolverem seus próprios protocolos, visando minimizar os riscos de intolerância e contemplando alguns aspectos mínimos já evidenciados por seus benefícios, tais como: cama elevada em *Trendelenburg* reverso entre 10 a 25 graus, uso de agentes procinéticos e interrupção da NE antes da mobilização para posição prona ou supina (MARTINDALE *et al.,* 2020*;* BARAZZONI *et al.,* 2020; CAMPOS *et al*., 2021; CCSG, 2020).

2.3.3 Histórico das evidências até o momento

Desde 2001, cinco estudos prospectivos, observacionais, um retrospectivo e um estudo randomizado investigaram o uso de NE em pacientes ventilados mecanicamente e que necessitaram de posição prona.

O estudo prospectivo cruzado inicial envolveu 19 pacientes que receberam NE usando o mesmo protocolo de alimentação nas posições prona e supina, demonstrando nenhuma diferença no VRG aferido em 3 ou 6 horas entre as posições. Todos os pacientes foram estudados por 6 horas em decúbito dorsal, seguidos imediatamente por 6 horas em decúbito ventral ou vice-versa. A velocidade de infusão da alimentação permaneceu inalterada durante o período de estudo e a cama foi elevada em ambas as posições até um máximo de 30 graus. Com relação às medicações, 10 dos 19 pacientes receberam cisaprida devido a um VRG superior a 150ml em 6 horas, todos os pacientes foram tratados com dopamina e sedados apenas quando necessário, por decisão do médico assistente. Morfina com midazolam em infusão contínua foi a sedação padrão, sendo necessária somente na PP (VAN DER VOORT; ZANDSTRA, 2001).

Em 2004, Reignier *et al.* (2004) avaliaram 71 pacientes adultos (37 em posição supina e 34 em posição prona) em ventilação mecânica e utilizaram um desenho prospectivo e comparativo. Uma bomba de infusão foi utilizada para a infusão da NE das 18h ao meio-dia do dia seguinte, exceto nos pacientes tratados com insulina, que foram alimentados continuamente A velocidade de infusão da NE foi de 30 mL/h no

primeiro dia, progredindo 30 mL/h diariamente até o quarto dia. A meta era administrar 500 mL no primeiro dia, 1.000 mL no segundo dia, 1.500 mL no terceiro dia e 2.000 mL no quarto e quinto dias. A tolerância à NE foi avaliada com base nas aferições repetidas do VRG e nos registros de episódios de vômitos. Todos os pacientes foram sedados com midazolam e fentanil. Os autores tiveram como resultado que a posição prona levou a ocorrência significativamente maior de VRG em comparação com a posição supina no dia 1 ($p=0,001$), dia 2 ($p=0,001$) e dia 4 ($p<0,01$) do estudo de 5 dias; resultando em subalimentação nos pacientes em decúbito ventral comparando com pacientes em decúbito dorsal ($p<0,05$).

Para melhorar a oferta de NE na posição prona, 6 anos após o trabalho anterior, o mesmo grupo desenvolveu um protocolo de NE em pacientes sob ventilação mecânica e em posição prona, incluindo agente procinético profilático e elevação da cama (*Trendelenburg* reverso a 25 graus). Os autores conseguiram demonstrar aumento no volume de NE recebido ($p< 0,001$), sem aumento no VRG ($p=0,6$), vômitos ($p=0,5$) ou pneumonia associada à ventilação mecânica ($p=0,81$) (REIGNIER *et al.*, 2010).

No trabalho randomizado de Sams *et al.* (2012), a fim de determinar a diferença na incidência de microaspiração, os pacientes com SDRA e em posição prona foram randomizados para NE em posição gástrica (n=9) ou pós-pilórica (n=11). Se o paciente tivesse alguma intolerância à NE (vômito e franca aspiração, distensão abdominal, diarreia intratável) ele era removido do estudo. Nenhuma outra informação sobra a TNE foi informada. Amostras diárias de secreção traqueal foram coletadas para detectar presença de pepsina. Esta esteve presente em 22% dos pacientes com sonda em posição gástrica e 20% dos pacientes com sonda em posição pós-pilórica ($p=1,0$), suportando a hipótese dos autores de que a localização do sonda de alimentação não altera o risco de microaspiração para pacientes que necessitam da PP, não devendo-se adiar a NE durante a tentativa de colocação da sonda em posição pós-pilórica.

Em 2016, temos a publicação de Saez de La Fuente *et al.* (2016), observacional, prospectivo e com delineamento cruzado, com 34 pacientes em PP e *Trendelenburg* reverso a 10 graus, onde a NE foi infundida através de posicionamento gástrico, sem uso profilático de agente procinético. A NE foi iniciada após verificação prévia da tolerância gastrointestinal (aferição de VRG <200 mL em resposta a 100 mL de água administrados por via nasogástrica em 2 intervalos de 3 horas). As

formulações foram infundidas ao longo de 24 horas por bombeamento contínuo, sendo ajustadas para atingir gradualmente 100% da meta de energia em etapas diárias de 25% durante os primeiros 4 dias. O VRG foi verificado a cada 6 horas no primeiro dia de NE, a cada 12 horas no segundo dia e diariamente a partir do terceiro dia. Os autores não encontraram diferença significativa no VRG diário quando os pacientes estavam em posição prona em comparação com a posição supina (p=0,054). Além disso, os pacientes em posição supina tiveram menos complicações (VRG elevado, vômitos e regurgitação) do que aqueles alimentados em posição prona; porém sem resultados estatisticamente significativos (p=0,39; p=0,53 e p=0,51; respectivamente).

Lucchini *et al.* (2017), em estudo observacional retrospectivo (n=25, pacientes com SDRA em VM e com TNE contínua), também verificaram que a administração da TNE durante a posição prona não promoveu aumento significativo do VRG em comparação à posição supina (p=0,73). Neste trabalho a cabeceira da cama foi mantida elevada a pelo menos 15 graus, VRG mensurado a cada 3 horas, sendo a dieta interrompida se VRG maior que 300mL.

Por fim, em estudo mais recente (n=47, observacional, prospectivo), os pesquisadores estudaram a viabilidade e a tolerância da NE em pacientes críticos com SDRA, em VM e posição prona. A alimentação nasogástrica ou orogástrica foi realizada em método contínuo, os procinéticos não foram empregados rotineiramente e foram usados a critério do médico. O VRG foi registrado a cada 6 horas e a velocidade de infusão foi ajustada de forma protocolizada a cada 6 horas com base nos valores de VRG. Se o VRG fosse <250 ml, a NE permanecia na mesma proporção ou era progredida. Se o VRG fosse >250 ml a NE era reduzida. A interrupção da NE por uma hora seguida foi recomendada para VRG > 300ml, sendo reintroduzida a uma velocidade reduzida juntamente com a administração de agente procinético. Os pacientes em posição supina foram mantidos em decúbito a 30 graus, enquanto aqueles em posição prona permaneceram em *Trendelenburg* reverso a 15 graus (SAVIO *et al.*, 2021). Estes autores não encontraram diferença na tolerância à NE entre o grupo em posição supina e posição prona quando analisado o VRG (mais de 250ml), vômitos ou diarreia. Embora os resultados não tenham sido clinicamente significativos, aumento estatisticamente significativo do VRG foi encontrado quando os pacientes estavam em posição prona em comparação com a posição supina (5,3 ± 3,9 ml; 15 ± 18,5 mL, respectivamente, p=0,03). Além disso, a posição prona não

teve interrupções da NE devido a diarreia, gastroparesia ou êmese, enquanto a posição supina teve a NE desligada para gastroparesia (6,6%) e êmese (1,4%) (p=0,344).

Revisões anteriores já discutiram sobre a literatura disponível acerca do efeito da administração da NE em pacientes críticos em posição prona (tolerância gastrointestinal e desfechos clínicos) como sendo escassa e com qualidade metodológica questionável, comprometendo a veracidade dos achados. A maioria dos estudos não é randomizada ou com cegamento, apresenta tamanho amostral reduzido e amplo intervalo de confiança dos resultados (LINN, BECKETT e FOELLINGER, 2015; MACHADO, RIZZI e SILVA, 2020; BEHRENS *et al.,* 2021; BROWN *et al.*, 2022).

Há variabilidades no desenho dos estudos, os que são de delineamento cruzado, a ordem das intervenções não é aleatória, a incidência de PAV e outros desfechos, como óbito, é avaliada em poucos trabalhos e nenhum dos estudos apresenta resultados de análise multivariada com ajuste para potenciais confundidores (LINN, BECKETT e FOELLINGER, 2015; MACHADO, RIZZI e SILVA, 2020).

3. MATERIAL E MÉTODOS

Trata-se de um estudo de coorte prospectivo realizado em uma UTI Respiratória de um hospital terciário de Curitiba-Paraná, Brasil, aprovado pelo Comitê de Ética em Pesquisa (n° 4.284.467) (ANEXO 1).

Foram avaliados pacientes internados entre o período de março de 2020 a janeiro de 2021, com idade superior a 18 anos, de ambos os sexos, com diagnóstico de COVID-19 e SDRA, submetidos à ventilação mecânica invasiva, que necessitaram ou não da manobra de prona, sendo a amostra por conveniência. Foram excluídos pacientes não submetidos à terapia nutricional enteral, pós cirúrgicos, gestantes e puérperas, ou falta de dados no prontuário.

Os pacientes foram acompanhados desde o momento da admissão na UTI até a alta para a enfermaria ou óbito. Os dados foram coletados do prontuário físico e eletrônico do paciente, além das fichas de avaliação e acompanhamento nutricional. O Índice de Comorbidade de Charlson (ICC) foi utilizado como escore de gravidade (CHARLSON, 1987).

Variáveis de desfecho, incluindo dias em VM, dias na UTI, dias de hospitalização e mortalidade foram coletadas nos prontuários. A incidência de PAV foi obtida no registro da comissão de controle de infecção hospitalar.

3.1 MANEJO RESPIRATÓRIO

A SDRA foi classificada, pela equipe médica responsável, segundo definições de Berlim (RANIERI *et al.*, 2012). Para este estudo foi realizada a coleta do menor valor de PaO_2/FiO_2 dentro de 24 horas pós intubação orotraqueal ou de internação na UTI, considerando as admissões de pacientes já intubados previamente.

A PP indicada conforme protocolo institucional, seguindo critérios internacionais de PP em SDRA (GUÉRIN *et al.,* 2013). A manobra foi realizada por equipe multiprofissional treinada, seguindo o protocolo operacional padrão do hospital, o qual segue o método em envelope.

Foram utilizados coxins na altura da pelve e tórax, visando alívio da pressão abdominal, em região tibial para garantir posicionamento anatômico dos pés e demais coxins conforme necessidade para alinhamento adequado do paciente.

O tempo total de permanência em PP era definido pela equipe multiprofissional, conforme resposta clínica do paciente à estratégia, sendo mantido o posicionamento por um período mínimo de 16 horas, exceto em ocorrência de grave instabilidade hemodinâmica.

3.2 MANEJO MEDICAMENTOSO

Sedação e uso de bloqueador neuromuscular (BNM) foram baseados nos protocolos da UTI.

O volume total administrado de cada droga foi coletado do relatório diário da enfermagem, que registra este dado a cada 2 horas. A diluição foi calculada conforme protocolo da UTI e utilizada na análise estatística a quantidade total do medicamento e sua exposição ao paciente em 24 horas.

3.3. TERAPIA NUTRICIONAL ENTERAL

A sonda nasogástrica ou orogástrica foi sempre introduzida pelo enfermeiro responsável e a ponta do catéter alocada em posição gástrica. A NE foi iniciada o mais precoce possível, dentro 12 a 48h.

A composição da TNE foi sempre prescrita pelos nutricionistas à beira leito, conforme protocolo do serviço de nutrição na pandemia. Para obesos e não obesos, os cálculos geralmente visavam a meta energética de 15-20 kcal/kg/dia na primeira semana, evoluindo para 25kcal/kg/dia de acordo com o quadro clínico do paciente (MARTINDALE *et al.,* 2020). As metas foram ajustadas para 30kcal/kg/dia, conforme dados anteriores para a fase de reabilitação (VAN ZANTEN, DE WAELE, WISCHMEYER, 2019), desde que não houvesse contraindicação clínica. Para pacientes com IMC <30kg/m^2, o peso corporal atual/real, relatado ou estimado (com medidas antropométricas (CHUMLEA *et al*., 1988) ou por inspeção visual do IMC (GARROW, WEBSTER, 1985) foi usado para aplicar kcal/kg/dia como mencionado acima (MARTINDALE *et al.,* 2020*;* VAN ZANTEN, DE WAELE, WISCHMEYER, 2019). Para IMC >30 kg/m2, foi considerado o peso ideal (MARTINDALE *et al.,* 2020). A altura foi estimada pela altura do joelho (CHUMLEA, ROCHE, STEINBAUGH, 1985).

As calorias não nutricionais foram consideradas (propofol: 1,1 kcal/ml – e soro glicosado: 3,4 kcal/grama de glicose), o citrato não foi utilizado na terapia de substituição renal (VAN ZANTEN, DE WAELE, WISCHMEYER, 2019).

A proteína foi prescrita de forma gradativa, objetivando as seguintes metas: <0,8 g/kg/dia, 1º e 2º dias; 0,8 a 1,2g/kg/dia, 3º ao 5º dia; e >1,2 g/kg/dia a partir do 5º dia (KOEKKOEK *et al.*,2019), podendo chegar até 2,0 g/kg/dia (MARTINDALE *et al.,* 2020). Na fase de reabilitação, a oferta proteica poderia chegar a 2,0-2,5 g/kg/dia (VAN ZANTEN, DE WAELE, WISCHMEYER, 2019).

Para pacientes obesos, foi considerada a seguinte recomendação: IMC entre 30-40 kg/m^2 (2g/Kg peso ideal) e IMC >40 kg/m^2 (2,5g/Kg peso ideal), sendo também prescrita de forma gradativa (MARTINDALE *et al.,* 2020).

As fórmulas enterais (poliméricas, oligoméricas, com densidade variando desde 1,0 a 2,0 kcal/ml) foram prescritas de forma individualizada e considerando a disponibilidade. Estas foram administradas por bomba de infusão contínua durante 22h/dia. Enquanto os módulos de proteína (à base de soro do leite e/ou de caseinato de cálcio diluídos em água) foram administrados de forma fracionada, em intervalos pré-estabelecidos, pelo método gravitacional, com ou sem interrupção da administração das fórmulas enterais. A velocidade foi determinada de maneira progressiva com base na tolerância do paciente.

Foi considerada obstipação "a ausência de eliminação de fezes por 3 ou mais dias consecutivos" (MOSTAFA *et al.,* 2003).

Os registros de presença de IGI também foram analisados. As IGI relacionadas à PP foram: 1. Presença de VRG durante a PP; 2. Vômito: retorno de grande volume de fórmula enteral expelida pela cavidade bucal; 3. Regurgitação da dieta: fórmula enteral encontrada na cavidade bucal ou nasal.

A administração de TNE foi registrada até sua suspensão definitiva, sendo a sua adequação calculada diariamente pelo nutricionista de forma individualizada e apresentada como volume de NE infundido.

3.4 PROTOCOLO DA TERAPIA NUTRICIONAL ENTERAL EM POSIÇÃO PRONA

O protocolo foi desenvolvido pela autora deste trabalho, baseando-se em aspectos mínimos já evidenciados por seus benefícios e incluiu o treinamento do

mesmo à equipe de enfermagem. Além disso, a equipe também foi treinada para administração das fórmulas enterais e módulos proteicos; registro do volume total de infusão da NE e módulos. O monitoramento diário do manejo da TNE foi realizado pelos nutricionistas e enfermeiros durante todo o internamento na UTI e registrado no prontuário, assim como, a checagem da administração de procinéticos durante a internação. O protocolo determinava que em posição supina, a cabeceira da cama fosse mantida em decúbito a 30 graus. Em PP, a cama foi mantida em *Trendelenburg* reverso a pelo menos 10 graus (MARTINDALE *et al.,* 2020).

A prescrição nutricional era a mesma para o paciente em posição supina ou prona. Uma única modificação realizada foi no volume de diluição dos módulos a base de soro do leite na PP, padronizados para no máximo 100ml (diluição máxima de 40% do produto).

Para os casos de pacientes já recebendo a TNE antes da manobra prona, os seguintes processos foram seguidos:

1. Dieta enteral foi interrompida 1h antes da manobra e reiniciada 1h após o posicionamento.
2. Não havendo contraindicação clínica, a mesma velocidade de infusão que vinha recebendo em posição supina era mantida, não ultrapassando 45ml/h.

Em caso de ocorrência de regurgitação alimentar, vômito ou estase, a NE era interrompida, a prescrição de procinéticos era revisada, a sonda aberta em frasco coletor e, de acordo com o VRG, as seguintes condutas eram tomadas:

1. Se VRG>500ml em 6 horas: TNE era descontinuada
2. Se VRG<500ml em 6 horas: TNE era religada em menor velocidade de infusão – 23ml/h - até reavaliação do nutricionista.

3.5 ANÁLISE ESTATÍSTICA

Os pacientes foram divididos em 2 grupos: grupo prona (GP), no qual todos os integrantes foram alocados em posição prona em algum momento da internação e grupo supina (GS), cujos indivíduos mantiveram-se durante toda a internação em posição supina.

Todas as variáveis contínuas foram avaliadas quanto à normalidade. As variáveis que não seguiram a distribuição normal foram analisadas com o teste U de Mann-Whitney. Outras variáveis foram analisadas por teste t de amostra independente.

Os dados com distribuição não normal são apresentados como medianas. Não foi realizada análise de poder da amostra devido à novidade da doença durante o período de observação.

As análises foram conduzidas no programa estatístico "R" (R CORE TEAM, 2020). Um P bicaudal <0,05 foi considerado estatisticamente significativo.

Modelos de regressão linear univariados foram testados para verificar o efeito de cada variável específica sobre o desfecho. Modelo de regressão múltipla foi utilizado para analisar quais fatores que contribuíram para as IGI, estimando a Razão de Chance e Intervalos de Confiança a 95%.

Os modelos lineares generalizados foram ajustados no pacote base, enquanto os modelos com efeitos mistos foram ajustados com o pacote "lme4" (BATES *et al.,* 2015).

Para avaliação do efeito dos medicamentos sob as IGI, foi utilizado um modelo de regressão da classe quasipoisson, com função de ligação logarítmica, devido a superdispersão da variável resposta. Nos modelos de regressão citados anteriormente, foi considerada a contagem de intercorrências totais ao nível de indivíduo durante o período de internamento do paciente.

4 APRESENTAÇÃO DOS RESULTADOS

Apresentam-se nas páginas seguintes o artigo que foi submetido em 12/04/2022 à revista *Clinical Nutrition Open Science*, com título "*Administration of enteral nutrition and gastrointestinal complications in COVID-19 critical patients in prone position*". Este artigo foi aceito em 20/08/2022 e publicado em 28/08/2022 online - https://www.sciencedirect.com/science/article/pii/S2667268522000444.

ADMINISTRATION OF ENTERAL NUTRITION AND GASTROINTESTINAL COMPLICATIONS IN COVID-19 CRITICAL PATIENTS IN PRONE POSITION

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 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.

Keyword: COVID-19; prone position; enteral nutrition.

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 to 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[11,12,13].

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 ≥ 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 to 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 to 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:

3. Enteral diet was paused 1h before the maneuver and restarted 1h after positioning
4. 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 "lme4" 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.

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).

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/m²)[a]	30,1±7,6	32,1±8,2	28,4 ±6,9	0,031
PaO_2/FiO_2 ratio[b*]	168 (58-420)	167 (58-284)	169,5 (62-420)	0,286
PaO_2/FiO_2 ratio <100 n (%)*	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.

[a] Mean±SD

[b] Median (interquartile range)

* n=108

Significant results (p<0,05).

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.

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 ($p<0.05$).

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 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).

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).

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)[26,27,28] 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.

Funding

The authors did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors for this manuscript.

Conflict of interests

The authors declare no conflict of interest.

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

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5 CONSIDERAÇÕES FINAIS

Apesar de poderem ser atribuídos a outros possíveis fatores de risco, é altamente provável que a PP foi um fator determinante das intolerâncias à NE. Porém o protocolo de manejo da TNE em PP utilizado neste estudo (seguindo medidas profiláticas e monitoramento rigoroso da tolerância à NE) mostrou-se uma alternativa efetiva e segura para manter a TNE de qualidade nos pacientes criticamente enfermos com COVID-19 sob VM, podendo este compartilhamento de experiência ajudar outros centros na efetividade da TNE em PP.

Além disso, a PP mostrou-se um fator de risco para PAV, porém não agravada pelo uso da TNE conforme protocolo utilizado neste trabalho.

5.1 RECOMENDAÇÕES PARA TRABALHOS FUTUROS

É possível observar que alguns trabalhos retrospectivos e pequenos estudos prospectivos mostraram que a NE durante a PP não está associado a um maior risco de intolerância gastrointestinal ou complicação pulmonar. Porém, uma sugestão para o futuro é a ampliação do número amostral deste estudo prospectivo, já que o momento da pandemia nos proporcionou uma frequência elevada deste cenário e a possibilidade de compreender a melhor estratégia para a TNE na PP.

Ensaios randomizados controlados que incluam uma quantidade significativa de casos precisam ser conduzidos para determinar a real viabilidade, tolerância e eficácia da NE em pacientes críticos em PP.

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ANEXO 1 – APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA

CEP/HC/UFPR

HOSPITAL DE CLÍNICAS DA UNIVERSIDADE FEDERAL DO PARANÁ - HCUFPR

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Perfil nutricional de pacientes infectados com SARS-CoV-2 que necessitaram de assistência hospitalar.

Pesquisador: Estela Iraci rabito

Área Temática:

Versão: 2

CAAE: 35738620.8.0000.0096

Instituição Proponente: Hospital de Clínicas da Universidade Federal do Paraná

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.284.467

Apresentação do Projeto:

Observacional, retrospectivo e prospectivo de caráter longitudinal que será realizado com pacientes internados com suspeita de SARS-CoV-2 até 24 - 48 horas no Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC - UFPR). A amostra será composta por aproximadamente 300 pessoas internadas infectadas com SARS-CoV-2, nas unidades UTI COVID 1, 2, 4 e 6 com idade superior a 18 anos, de ambos os sexos. Equipe da pesquisa: Estela Iraci Rabito, Jessica Alves de Paula e Sandra Regina Justino, Gabriela Lazzaron e Luiza da Silva Leite.

Objetivo da Pesquisa:

mantido

Avaliação dos Riscos e Benefícios:

mantidos

Comentários e Considerações sobre a Pesquisa:

propõe através de emenda alteração do método (também retrospectivo), inclusão de pesquisadores na equipe, alteração do numero de participantes (aumento), inclusão das UTIs COVID 4 e 6.

Considerações sobre os Termos de apresentação obrigatória:

apresentou projeto atualizado, alterações na PB, dispensa do TCLE (retrospectivos), TCLE nova versão.

Endereço: Rua Gal. Carneiro, 181
Bairro: Alto da Glória **CEP:** 80.060-900
UF: PR **Município:** CURITIBA
Telefone: (41)3360-1041 **Fax:** (41)3360-1041 **E-mail:** cep@hc.ufpr.br

Continuação do Parecer: 4.284.467

Conclusões ou Pendências e Lista de Inadequações:

emenda aprovada

Considerações Finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa em Seres Humanos do HC-UFPR, de acordo com as atribuições definidas na Resolução CNS 466/2012 e na Norma Operacional Nº 001/2013 do CNS, manifesta -se pela aprovação da Emenda.

Solicitamos que sejam apresentados a este CEP, relatórios semestrais sobre o andamento da pesquisa, bem como informações relativas às modificações do protocolo, cancelamento, encerramento e destino dos conhecimentos obtidos. Manter os documentos da pesquisa arquivados.

É dever do CEP acompanhar o desenvolvimento dos projetos, por meio de relatórios semestrais dos pesquisadores e de outras estratégias de monitoramento, de acordo com o risco inerente à pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1615732_E1.pdf	26/08/2020 09:20:16		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	dispensa_TCLE_emenda_1_assinatura.pdf	26/08/2020 09:15:12	Estela Iraci rabito	Aceito
Declaração de Pesquisadores	Declaracao_compromisso_equipe_emenda_01assinatura.pdf	26/08/2020 09:14:47	Estela Iraci rabito	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Dispensa_TCLE_emenda_4assinaturas.pdf	24/08/2020 17:46:25	Estela Iraci rabito	Aceito
Declaração de Pesquisadores	Declaracao_compromisso_equipe_emenda_04assinaturas.pdf	24/08/2020 17:46:02	Estela Iraci rabito	Aceito
Outros	Concordancia_UTICOVID_emenda.pdf	24/08/2020 17:44:33	Estela Iraci rabito	Aceito
Outros	10_DISPENSA_TERMO_CONSENTIMENTO_emenda.docx	24/08/2020 09:55:04	Estela Iraci rabito	Aceito
Outros	1_MODELO_CARTA_EMENDA_1.docx	24/08/2020 09:53:03	Estela Iraci rabito	Aceito
Outros	carta_encaminhamento_emenda.pdf	24/08/2020	Estela Iraci rabito	Aceito

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Bairro: Alto da Glória **CEP:** 80.060-900
UF: PR **Município:** CURITIBA
Telefone: (41)3360-1041 **Fax:** (41)3360-1041 **E-mail:** cep@hc.ufpr.br

Outros	carta_encaminhamento_emenda.pdf	09:52:33	Estela Iraci rabito	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_V2_emenda.docx	24/08/2020 09:50:42	Estela Iraci rabito	Aceito
Projeto Detalhado / Brochura Investigador	Protocolo_brochura_emenda1.docx	24/08/2020 09:49:47	Estela Iraci rabito	Aceito
Projeto Detalhado / Brochura Investigador	Protocolo_brochura.doc	30/06/2020 10:22:33	Estela Iraci rabito	Aceito
Outros	CHECK_LIST_DOCUMENTAL_v_2.pdf	30/06/2020 10:21:47	Estela Iraci rabito	Aceito
Outros	COMPROMISSO_EQUIPE_1.pdf	22/05/2020 08:50:11	Estela Iraci rabito	Aceito
Outros	CONCORDANCIA_UTI.pdf	21/05/2020 18:57:37	Estela Iraci rabito	Aceito
Outros	CONCORDANCIA_NUTRICAO.pdf	21/05/2020 18:57:20	Estela Iraci rabito	Aceito
Outros	MODELO_DECLARACAOO_AUSENCIA_CUSTOS_CHC_UFPR.pdf	21/05/2020 18:56:27	Estela Iraci rabito	Aceito
Outros	2_CARTA_ENCAMINHAMENTO_PESQUISADOR_AO_CEP.pdf	21/05/2020 18:55:01	Estela Iraci rabito	Aceito
Declaração de Pesquisadores	5_DECLARACAO_COMPROMISSO_EQUIPE_PESQUISA.doc	21/05/2020 18:53:50	Estela Iraci rabito	Aceito
Declaração de concordância	Concordancia_infectologia.pdf	21/05/2020 18:50:57	Estela Iraci rabito	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_04maio.docx	21/05/2020 18:50:37	Estela Iraci rabito	Aceito
Folha de Rosto	Folha_de_Rosto_assinada.pdf	21/05/2020 18:49:23	Estela Iraci rabito	Aceito
Outros	Planilha_Coleta.xlsx	05/05/2020 10:31:25	Estela Iraci rabito	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CURITIBA, 17 de Setembro de 2020

Assinado por:
maria cristina sartor
(Coordenador(a))

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ANEXO 2 – ARTIGO NA ÍNTEGRA PUBLICADO NA *CLINICAL NUTRITION OPEN SCIENCE*

ALVES DE PAULA, J. et al. Administration of enteral nutrition and gastrointestinal complications in Covid-19 critical patients in prone position. **Clin Nutr Open Sci.** v. 45, p. 80-90, 2022.

Disponível em: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9420200/*

ELSEVIER

Clinical Nutrition Open Science

Available online 28 August 2022

In Press, Journal Pre-proof

Original Article

ADMINISTRATION OF ENTERAL NUTRITION AND GASTROINTESTINAL COMPLICATIONS IN COVID-19 CRITICAL PATIENTS IN PRONE POSITION

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Journal Pre-proof

ADMINISTRATION OF ENTERAL NUTRITION AND GASTROINTESTINAL COMPLICATIONS IN COVID-19 CRITICAL PATIENTS IN PRONE POSITION

Jéssica Alves de Paula, RD, Estela Iraci Rabito, RDPhD, Sandra Regina Justino, RDPhD, Luíza Silva Leite, RDMsC, Danielle Dantas, RDMsC, Jéssica Sayume Makiyama da Silva, RD, Larissa Farinha Maffini, RD, Odery Ramos Júnior, MDPhD

PII: S2667-2685(22)00044-4

DOI: https://doi.org/10.1016/j.nutos.2022.08.003

Reference: NUTOS 244

To appear in: *Clinical Nutrition Open Science*

Received Date: 12 April 2022

Revised Date: 20 August 2022

Accepted Date: 20 August 2022

Please cite this article as: Alves de Paula J, Rabito EI, Justino SR, Leite LS, Dantas D, Makiyama da Silva JS, Maffini LF, Júnior OR, ADMINISTRATION OF ENTERAL NUTRITION AND GASTROINTESTINAL COMPLICATIONS IN COVID-19 CRITICAL PATIENTS IN PRONE POSITION, *Clinical Nutrition Open Science*, https://doi.org/10.1016/j.nutos.2022.08.003.

ADMINISTRATION OF ENTERAL NUTRITION AND GASTROINTESTINAL COMPLICATIONS IN COVID-19 CRITICAL PATIENTS IN PRONE POSITION

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 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.

Keyword: COVID-19; prone position; enteral nutrition.

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 to 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[11,12,13].

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 ≥ 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 to 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 to 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].

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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 "lme4" 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.

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 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)[26,27,28] 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

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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.

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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.

Funding

The authors did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors for this manuscript.

Conflict of interests

The authors declare no conflict of interest.

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

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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/m²)[a]	30,1±7,6	32,1±8,2	28,4 ±6,9	0,031
PaO_2/FiO_2 ratio[b*]	168 (58-420)	167 (58-284)	169,5 (62-420)	0,286
PaO_2/FiO_2 ratio <100 n (%)*	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.

[a] Mean±SD

[b] Median (interquartile range)

* n=108

Significant results (p<0,05).

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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 ($p<0.05$).

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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 ($p<0.05$).