Associations between enteral nutrition and outcomes in the SUP-ICU trial

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RESEARCH ARTICLE

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Associations between enteral nutrition and outcomes in the SUP-ICU trial: Protocol for exploratory post hoc analyses

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Abstract

Critically ill patients are at risk of gastrointestinal (GI) bleeding. Counter measures to minimise this risk include the use of pharmacological stress ulcer prophylaxis (SUP). The effect of enteral nutrition as SUP on GI bleeding event rates is unknown. There are conflicting data describing the effect of co-administration of enteral nutrition with pharmacological SUP, and there is substantial variation in practice. We aim to conduct an exploratory post hoc analysis to evaluate the association of enteral nutrition with clinically important GI bleed rates in ICU patients included in the SUP-ICU trial, and to explore any interactions between enteral nutrition and pharmacologic SUP on patient outcomes. The SUP-ICU trial dataset will be used to assess if enteral nutrition is associated with the outcomes of interest. Extended Cox models will be used considering relevant competing events, including treatment allocation (SUP or placebo) and enteral nutrition as a daily time-varying covariate, with additional adjustment for severity of illness (SAPS II). Results will be presented as adjusted hazard ratios for treatment allocation and enteral nutrition, and for treatment allocation and enteral nutrition considering potential interactions with the other variable, all with 95% confidence intervals and p-values for the tests of interaction. All results will be considered as exploratory only. This post hoc analysis may yield important insights to guide

practice and inform the design of future randomised clinical trial investigating the effect of enteral nutrition on GI bleeding.

KEYWORDS
enteral nutrition, pantoprazole, protocol, proton pump inhibitor, stress ulcer prophylaxis

1 | INTRODUCTION

Critically ill patients are at risk of stress-related gastrointestinal (GI) bleeding events. These events have been associated with adverse outcomes, including increased risk of death.[1] Measures to prevent GI bleeding in critically ill patients are widely promoted and centre on the use of acid-suppressing therapy as stress ulcer prophylaxis (SUP).[2]

The role of enteral feeding to prevent GI bleeding has also been investigated.[3,4] However, a systematic review has concluded that there is not enough high-quality data to make inferences about using enteral feeding as SUP.[5] Early enteral feeding in critical care is considered desirable for a variety of other reasons and so is promoted through international guidelines and is in widespread use.[2,6,7]

Separate from any possible effect of enteral feed alone, the interaction between acid suppressant SUP and enteral feed has also been studied. A systematic review and meta-analysis in 2010 included trials investigating pharmacological SUP utilising histamine-2-receptor antagonists (H2RA). It compared the outcomes of SUP in trial cohorts that received feed alongside H2RA with cohorts that did not. The review concluded that concomitant SUP and enteral feed may lead to harm through increased pneumonia rates and increased hospital mortality.[8]

Small trials have been undertaken to compare GI bleeding rates in patients with pharmacological SUP plus early enteral nutrition compared with placebo plus early enteral nutrition. These trials found no statistically significant differences in GI bleeding rates[9,10]; however, they were underpowered with risk of Type 2 error.

In a systematic review and meta-analysis from 2018, Huang et al.[11] included trials investigating H2RA and proton pump inhibitors (PPI) for pharmacological SUP, to look at the effect of concomitant enteral feed. The authors found no statistically significant difference in haemorrhage or mortality when feed was an independent variable, but there was a suggestion of increased risk of hospital-acquired pneumonia in the groups that received feed with pharmacological SUP. A similar systematic review and meta-analysis with trial sequential analysis also found that enteral nutrition did not statistically significantly affect outcomes of pharmacological SUP with respect to bleeding, and also found no statistically significant effect of nutrition with pharmacological SUP on pneumonia rates.[12] A further systematic review and meta-analysis found enteral nutrition was associated with decreased risk of clinically important GI bleeding after excluding trials with a high risk of bias.[13] There have been calls to prioritise research investigating the effect of enteral nutrition on the effects of gastric acid suppression with SUP.[14]

Despite this uncertainty, a recent international survey found that 32% of critical care units routinely ceased pharmacological SUP when enteral feeding is established, and a Canadian study found that acid suppressants for SUP were ceased in 22% of patients when they were no longer nil by mouth.[15,16]

Accordingly, there is a lack of agreement in clinical practice regarding the use of pharmacological SUP in relation to enteral feed, leading to variation in practice and calls for larger clinical trials.[17]

The SUP in the intensive care unit (SUP-ICU) trial was an international, blinded randomised controlled trial comparing the effects of prophylactic intravenous pantoprazole versus placebo on patient-important outcomes in 3298 adult ICU patients at risk of GI bleeding.[18] There was no overall statistically significant difference between groups in the primary outcome of mortality (31.1% vs. 30.4%, relative risk (RR) 1.02, 95% confidence interval [CI] 0.91–1.13). However, patients assigned to pantoprazole had lower rates of clinically significant GI bleeding when compared with patients assigned to placebo (2.5% vs. 4.2%, RR 0.58, 95% CI 0.40–0.86). Among others, data on enteral nutrition were also collected daily.[19]

We will therefore conduct an exploratory post hoc analysis to evaluate the association of feed on GI bleed rates in ICU patients included in the SUP-ICU trial, and to explore if feed modifies any such associations between pharmacologic SUP and patient outcomes and vice versa.

2 | METHODS

2.1 | Study design and data sources

An exploratory post hoc analysis of data from the SUP-ICU trial.[18,19] These analyses will not be conducted until after the protocol is accepted for publication in a peer-reviewed journal.

2.2 | Study setting and population

We will include all patients enrolled in the intention-to-treat population of the SUP-ICU trial.[18]

Full inclusion and exclusion criteria are described elsewhere.[19] Briefly, the SUP-ICU trial included adult (≥18 years old) patients acutely admitted to the ICU with one or more risk factors for GI bleeding. Exclusion criteria were mainly related to known recent GI bleeding, continuing use of PPIs/H2RAs or contraindications to the trial drug. In total, 3298 patients from 33 ICUs in 6 countries were

randomised between 4 January 2016 and 22 October 2017 in a 1:1 ratio to 40 mg pantoprazole or matching placebo, administered intravenously once daily during ICU admission for a maximum of 90 days (data on 3291 patients were available for analyses).[18]

2.3 | Research questions

1. Is there an association between the use of enteral nutrition and GI bleeding, all-cause mortality, or pneumonia in critically ill patients, when accounting for the use of SUP?
2. Are the potential associations of use of enteral nutrition modified by SUP with pantoprazole and vice versa in critically ill patients?

2.4 | Definitions

Definitions used for overt GI bleeding, clinically important GI bleeding, pneumonia and other outcomes are as described for the SUP-ICU trial,[18–20] and appear in the Appendix S1.

Any enteral nutrition: receipt of any dose of enteral feeding (including oral nutritional intake) during the day.

As there is some evidence that most patients achieve full/maximal enteral feeding within 2 days of commencing enteral feed,[21,22] we have defined sustained enteral nutrition as the receipt of enteral nutrition on each day and the day prior (i.e., 2 consecutive days).

2.5 | Data, outcomes and variables assessed

2.5.1 | Treatment allocation

Allocation to SUP or placebo.

2.5.2 | Baseline variables

Baseline variables are as described in the primary SUP-ICU trial report (Table 1),[18] and are listed in the Appendix S1; detailed definitions can be found elsewhere.[19,20]

2.5.3 | Daily variables

Use of enteral nutrition each day (y/n) in the ICU up to a maximum of 90 days.

2.5.4 | Outcomes

Primary outcome

Clinically important GI bleeding in the ICU within 90 days.

Secondary outcomes

Pneumonia in the ICU within 90 days.

All-cause mortality within 90 days.

2.6 | Sample size and power

The SUP-ICU trial enrolled for a fixed sample size of the 3350 randomised patients, and thus no formal power calculation for this secondary study has been made.

The number of events for some outcomes are limited, and enteral nutrition provision was not randomised, thus all analyses conducted in this study will be considered exploratory and interpreted with caution.

2.7 | Statistics

Baseline demographic and descriptive outcome data will be presented as medians with interquartile ranges for continuous data, and numbers with percentages for categorical data. Data will be presented stratified for the combinations of whether patients received enteral nutrition on the first study day and treatment allocation.

2.7.1 | Assessment of the association between the use of enteral nutrition and outcomes assessed

To assess if enteral nutrition is associated with the outcomes assessed, we will use extended Cox models with time-varying covariates[23] and competing events.[24] Models will include the use of enteral nutrition as a time-varying covariate (varying each day), treatment allocation (SUP or placebo, which affects the risk of clinically important GI bleeding[18,26]), and further adjusted for baseline SAPS II[25] as the use of enteral nutrition may be associated with severity of illness. For each outcome assessed, the following competing events will be considered with observations censored at the first competing event:

1. Mortality (for all other outcomes).
2. Clinically important GI bleeding (for all other outcomes, as clinically important GI bleeding is usually treated with PPI, with patients thus no longer generally adhering to the treatment allocation after bleeding).
3. ICU discharge (as daily data on enteral nutrition was not registered outside participating ICUs and use of acid suppressants was no longer controlled as part of the trial).

Results will be presented as adjusted hazard ratios (HRs) with 95% CIs and *p*-values for the associations of enteral nutrition and SUP with each outcome.

TABLE 1 Blank results table to be populated when analyses complete.

Outcome	Adjusted HR (95% CI, and *p*-value)						Test-of interaction between EN and treatment allocation
	EN	SUP	EN in patients allocated to SUP	EN in patients allocated to placebo	SUP in patients not receiving EN	SUP in patients receiving EN	
Clinically important GI bleeding	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	p = #
Pneumonia	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	p = #
All-cause mortality	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	X.XX (Y.YY – Z.ZZ p = #)	p = #

Abbreviations: 95% CI, confidence interval; EN, enteral nutrition; GI, gastrointestinal; SUP, stress ulcer prophylaxis with pantoprazole.

2.7.2 | Assessment of the potential interaction between enteral nutrition and SUP on the outcomes assessed

Secondarily, the outcomes will be assessed using similar models, also including interaction terms between enteral nutrition (time varying) and treatment allocation. Results will be presented as HRs with 95% CIs and *p*-values for the associations between enteral nutrition and SUP and the outcomes in each allocation group considering the interaction, with *p*-values for the interactions calculated using likelihood ratio tests.

2.7.3 | Assessment of model adequacy

The proportional hazards assumption (whether the effects of the included variables vary over time) will be assessed using scaled Schoenfeld residuals,[26] and handled if violated using either stratification (for SAPS II, categorised if relevant) or if necessary time-varying effects; if none of these methods work, alternative models will be considered.

Two-tailed *p*-values < .05 will be considered statistically significant and 95% CIs will be presented where appropriate. Despite the significance thresholds used, we will describe and interpret the results in terms of compatibility.[27] No corrections for multiple testing will be performed, but as stated above, all findings from this study will be considered exploratory and cautiously interpreted.

2.7.4 | Sensitivity analyses

As the enteral nutrition status was recorded as a daily binary yes/no, and clinical practice in many cases is to make decisions about SUP when the patient is in receipt of 'full enteral feed', rather than 'any enteral fed', we will repeat the analyses replacing enteral nutrition with sustained enteral nutrition. In addition, we will repeat the analyses of clinically important GI bleeding using overt GI bleeding.

2.7.5 | Missing data

The proportions of missing data for all variables assessed will be presented. Descriptive data will be based on complete cases only, with the proportions of missing data presented.

We know that 7.6% of SAPS II records are incomplete,[18] and as analyses are subject to adjustments for SAPS II, multiple imputation will be required and no complete case analyses will be conducted or presented. We will create 25 imputed datasets separately in each group.[28] Imputations will be performed using chained equations via the *mice* R package[29] using predictive mean matching for continuous variables and logistic regression for binary/categorical variables, with results combined as appropriate.[30] All outcomes listed above, the baseline variables listed in the Appendix S1, and the use of enteral

nutrition or not on day 1 will be included in the imputation models. We expect very limited missing daily data for enteral nutrition, and, for simplicity, will use last-value-carried-forward for these missing values before multiple imputation.

2.8 | Ethics and approvals

The SUP-ICU trial was approved by the Danish Health and Medicine Agency (2015030166), the Committees on Health Research Ethics in the Capital Region of Denmark (H-15003141) and the Danish Data Protection Agency (RH-2015-3,203,695). All necessary approvals in the other participating countries were obtained and the trial was registered at ClinicalTrials.gov (NCT02467621).[19]

2.9 | Reporting

The results will be submitted to an international peer-reviewed journal regardless of findings. Results will be reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[31] This protocol has to the furthest extent possible been written to comply with the STROBE statement.

3 | DISCUSSION

Clinically important GI bleeding due to stress ulceration in the ICU is uncommon. Nearly, three quarters of ICU patients are treated with pharmacologic SUP[32] although the publication of recent studies could have changed practice. Over 85% of critically ill patients receive enteral nutrition during their ICU stay[33] and clinical practice in nearly a third of ICUs is to stop pharmacologic SUP when enteral feed is established.[15] However, a possible prophylactic effect of enteral feed on GI bleeding from stress ulcers is uncertain. Potential interactions on patient outcomes (beneficial or harmful) between enteral nutrition and pharmacologic SUP also need to be explored. In the outlined study, we will attempt to further elucidate effects of enteral nutrition on GI bleeding and any potential interaction with pantoprazole in the SUP-ICU trial, as well as provide data that may inform future studies.

This study has several strengths; source data are from a recent, large, international, RCT with high generalisability. However, the event rate of clinically significant GI bleeding was low making these analyses prone to Type II error. Consequently, we will interpret results not only considering statistical significance, but also in terms of compatibility, as outlined above. Also, the use of feed recorded in the study was a binary 'fed vs. not-fed' record and not recorded at baseline (but daily), and so no determination can be made about any effect that proportion of daily feed target met has on outcomes, although a sensitivity analysis will be conducted to explore this further. We will only analyse according to assignment to SUP or placebo not actual SUP use, however, protocol violations in SUP-ICU were few and clinically important GI bleeding will be considered a competing event in all models.[18] Finally, the use of feed was not randomised leading to the potential for confounding, this study will thus only assess associations and not causal effects of enteral nutrition on the outcomes of interest. Although the use of enteral nutrition was not randomised, the blinded use of SUP or placebo is unlikely to have affected the decision to initiate feeding.

4 | CONCLUSION

We will use the SUP-ICU trial dataset to assess associations between enteral nutrition and GI bleeding, and to evaluate if the use of pharmacological SUP interacts with any such associations in critically ill patients. This exploratory post hoc analysis may yield important insights to guide practice and inform the design of future randomised clinical trial investigating the effect of enteral nutrition on GI bleeding.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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