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RESEARCH ARTICLE

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Prokinetic agents in adult intensive care unit patients (PATIENCE)—An international inception cohort study protocol

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Abstract

Background: Feeding intolerance is common in critically ill patients and can lead to malnutrition. Prokinetic agents may be used to enhance the uptake of nutrition. However, the evidence on the effectiveness and safety of prokinetic agents is sparse, and there is a lack of data on their use in intensive care units (ICU).

Methods: We will conduct an international 14-day inception cohort study of 1000 acutely admitted adult ICU patients. Data will be collected from ICU admission and

daily during ICU stay for up to 90 days. The primary outcome will be the proportion of ICU patients who receive prokinetic agents. Secondary outcomes include mortality, days alive without life support, days alive out of ICU, days alive out of hospital (all within 90 days) and the number of patients with one or more serious adverse events.

Results: We will present data on the use of prokinetic agents descriptively and use Cox regressions with death and ICU discharge as competing events to evaluate the association between patient characteristics and the use of prokinetic agents. We will use extended Cox models with time-varying covariates and linear regression models to assess the associations between the use of prokinetic agents and the secondary outcomes.

Conclusion: The outlined international cohort study will provide valuable epidemiological data on the use of prokinetic agents in adult, acutely admitted ICU patients.

KEYWORDS
cohort study, intensive care, prokinetic agents, protocol

1 | BACKGROUND

Sufficient uptake of nutrition depends on gastrointestinal (GI) function and motility, which is often impaired in critically ill patients.[1,2]

One strategy to improve nutrition uptake is to treat patients with prokinetic agents that directly or indirectly stimulate smooth muscle contractions in the upper GI tract. Current guidelines lack consistency in dosage and frequency and are based on low to moderate certainty evidence.[3,4] Additionally, prokinetic agents may have undesirable effects, and limited evidence supports their efficacy on clinically relevant outcomes.[2,5]

Epidemiological data on the use of prokinetic agents in adult intensive care unit (ICU) patients are sparse, and are required to inform the planning of a randomised clinical trial assessing the efficacy and safety of prokinetic agents in ICU patients. Therefore, we aim to assess the use of prokinetic agents in adult ICU patients, including the proportion of patients treated, the association with patient characteristics, and the association with patient-important outcomes.

1.1 | Research questions

1. What is the proportion of adult, acutely admitted ICU patients who receive prokinetic agents?
2. Which prokinetic agents and administrations are used (dose, frequency and duration)?
3. Are there associations between specific patient characteristics and the use of prokinetic agents?
4. Is treatment with prokinetic agents associated with patient-important outcomes?

1.2 | Hypothesis

We hypothesise that

1. approximately one out of four patients acutely admitted to the ICU receive prokinetic agents at least once during their ICU stay;
2. mechanical ventilation and emergency abdominal surgery are associated with the use of prokinetic agents;
3. erythromycin, metoclopramide, and domperidone are the most commonly used prokinetic agents in ICU, and there is practice variation in dose, frequency, and duration of treatment;
4. treatment with prokinetic agents is not associated with improved patient-important outcomes.

2 | METHODS

2.1 | Study design and setting

The planned study is an international inception cohort study. We will collect data prospectively and aim to include 1000 patients from participating ICUs in 12 countries (Denmark, Saudi Arabia, Poland, Switzerland, Estonia, Kuwait, Sweden, Finland, Great Britain, Spain, Iceland and the Netherlands).

The Management Committee will coordinate the study centrally in collaboration with national investigators from each participating country (the Management Committee and known national investigators and sites are listed in Appendices S2 and S3). Locally, the study will be managed and coordinated by a local investigator responsible for data collection and maintenance of study documentation. Figure 1 provides an overview of the study.

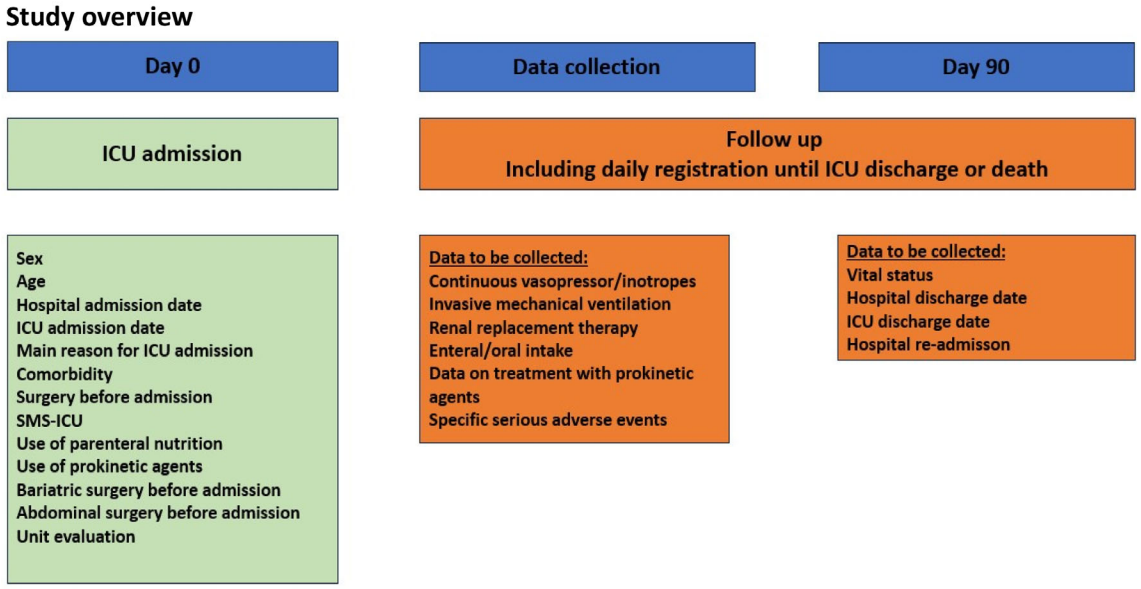

FIGURE 1 Study overview of the planned study. Patients will be included during a 14-day inception period between two dates defined by the management group. All acutely admitted adult patients will be screened for inclusion during this period. Patients will be followed daily during their ICU stay until day 90 when the follow-up data will be completed. Baseline values are registered at inclusion, and daily registrations are done in the ICU for a maximum of 90 days. ICU, intensive care unit; SMS-ICU, Simplified Mortality Score for the Intensive Care Unit.[8]

We will report the main manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The protocol is written in accordance with the STROBE statement, and the STROBE checklist is included in Appendix S1.[6]

2.2 | Approvals

The study is approved by the Danish Research Support Center, Region Zealand (EMN-2024-03449). The national investigators will obtain approvals from all required authorities in participating countries before patient enrolment. If required, local investigators will obtain informed consent. Due to the observational design, there are no treatment alterations or risks to the patients.

2.3 | Inclusion criteria

All adult patients (aged ≥18 years) who are acutely admitted to a participating ICU during the 14-day inception period will be screened for inclusion by local investigators.

Patients already in the ICU at the start of the inception period will not be screened for inclusion. Patients transferred from a non-participating ICU will be included if they meet the inclusion criteria.

2.4 | Exclusion criteria

Patients previously included in the study (patients who are readmitted during the study period will continue with data collection) and those for whom informed consent (when required) has not been obtained will be excluded. Furthermore, patients with planned ICU admissions, that is, after elective surgery, will be excluded.

2.5 | Outcomes measures

2.5.1 | Primary outcome

The primary outcome is the proportion of ICU patients receiving prokinetic agents.

2.5.2 | Secondary outcomes

Secondary outcomes:

1. 90-day mortality;
2. Days alive without life support (invasive mechanical ventilation, circulatory support or renal replacement therapy) within 90 days of inclusion;
3. Days alive out of ICU within 90 days of ICU inclusion;
4. Days alive out of hospital within 90 days of ICU inclusion;
5. Number of patients with one or more specific serious adverse events (SAE) during ICU stay: cardiac arrest, new cardiac arrhythmias requiring pharmacological treatment, extrapyramidal symptoms requiring pharmacological treatment, severe diarrhoea requiring treatment and vomiting with clinically significant aspiration requiring treatment.

The outcomes are defined in detail in Appendix S4.

2.6 | Data collection management

Data will be collected by local investigators and managed in an electronic case report form (eCRF) in the Research Electronic Data Capture (REDCap) database hosted at Region of Zealand, Denmark.[7]

Baseline data will include general patient and admission data, comorbidities, data on surgery, treatment with parenteral nutrition, use of prokinetic agents before admission, and the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)[8] (further specifications of baseline characteristics, including comorbidities, are provided in Appendix S5).

We will collect data from ICU admission until the conclusion of the 90-day follow-up period, discharge from ICU, or death, whichever comes first. If patients are readmitted to the ICU, data collection will continue. Daily data include the use of life support, nutrition intake data, treatment with prokinetic agents, and specific serious adverse events (further specifications and definitions of daily data are provided in Appendix S6).

Data on discharge and readmission will be collected as described in Appendix S7. The follow-up data will include vital status, discharge data, and readmission data (Appendix S8).

Data on participating sites, including type of hospital, size, and type of ICU, will be documented separately in REDCap (Appendix S9).

The local investigator will be responsible for data collection and their accuracy. Each investigator can only enter and read data for patients enrolled at their site. All included patients are assigned a unique study identification number, and we will store data as required by the data protection authorities. No data analyses will be carried out before the accuracy of the database has been assured.

2.7 | Statistical methods

2.7.1 | Sample size estimation

Based on an estimated overall prevalence of feeding intolerance of 25% in critically ill patients in the ICU[9,10] and presuming it corresponds approximately to the proportion of patients receiving prokinetic agents, we plan to include 1000 patients to determine the use of prokinetic agents with a 95% confidence interval (CI) of 22%–28%.

2.7.2 | Population to be analysed

We will analyse all included patients. We will present baseline data descriptively for all included patients stratified by any treatment with prokinetic agents or not during the ICU stay. Continuous variables will be described using medians with interquartile ranges, and categorical variables will be presented as counts with corresponding percentages.

2.7.3 | Description of the use of prokinetic

The type of prokinetic agents, dose, frequency, and duration will be presented descriptively.

2.7.4 | Association between patient characteristics and use of prokinetic agents

We will assess the association between baseline characteristics and the time to use of prokinetic agents with Cox proportional hazard models to compute hazard ratios (HRs) with 95% CIs. We will use time since inclusion as the time axis, and death and first ICU discharge will be considered competing events.[11] We will evaluate both crude and adjusted (for all other baseline variables mentioned) associations between treatment with prokinetic agents (dependent variable) and the following independent baseline variables: ICU admission type (acute abdominal surgery, acute surgery other than abdominal or medical), treatment with parenteral nutrition at ICU admission (Y/N), number of comorbidities as defined in Appendix S6 (categorised as 0, 1, 2 or 3+), invasive mechanical ventilation (Y/N), use of vasopressors/inotropes (Y/N), renal replacement therapy (Y/N) and SMS-ICU (continuous variable 0–42).

2.7.5 | Association between prokinetic agents and 90-day mortality

To assess the association between the use of prokinetic agents and mortality, we will employ a Cox proportional hazard model with prokinetic agents as a time-varying covariate as the treatment with prokinetic agents may change over time (treatment status can change from not receiving treatment to receiving treatment and vice versa).[12] We will adjust for country, SMS-ICU (continuous variable 0–42), comorbidities (0, 1, 2 or 3+) and ICU admission type (acute abdominal surgery, acute surgery other than abdominal or medical). We will consider the first discharge alive from the ICU as a competing event.[11] Results will be presented as adjusted HRs with 95% CIs.

2.7.6 | Association between prokinetic agents and specific serious adverse events

We will descriptively present the occurrence of each specific SAE stratified by the use of prokinetic agents. We will employ a Cox proportional hazard model as the one described above with treatment with prokinetic agents as a time-varying covariate to assess the association between treatment with prokinetic agents and specific SAEs.[12] We will assess all specific SAEs as a pooled outcome (i.e. as one or more of the listed SAEs) due to the expected low incidence of each SAE. In this case, death and first discharge from the ICU will be treated as competing events.[11] We will adjust analyses for country, SMS-ICU (continuous variable 0–42), comorbidities (0, 1, 2 or 3+), and ICU

admission type (acute abdominal surgery, acute surgery other than abdominal or medical).

The results will be presented as adjusted HRs with 95% CIs.

2.7.7 | Assessment of model adequacy

We will use scaled Schoenfeld residuals to evaluate the proportional hazard assumption (i.e. whether the effects of the included variables remain constant over time).[13] If there is evidence of violations of the proportional hazards assumption or for the non-linearity of continuous independent variables (assessed by including an additional non-linear term in the models), we will use either the addition of a non-linear term (e.g. log-transformation or adding a squared term), stratification, or time-varying effects. If none of the above approaches adequately addresses the violation of the model assumptions, alternative methods or models will be considered.[13]

2.7.8 | Association between prokinetic agents and other secondary outcomes

The association between treatment with prokinetic agents at any time and the secondary outcomes (days alive without life support, days alive out of ICU, and days alive out of hospital) will be analysed using linear regression. Patients who die during follow-up will be assigned the worst possible outcome (0 days), as commonly done in previous studies.[14] Secondary analyses will be made using the actual number of days, regardless of vital status.[15,16] Results will be presented as mean differences (MDs) with 95% CIs. Due to the expected non-normality of the residuals due to the highly non-normal outcome distribution, we will use non-parametric bootstrapping with 50,000 resamples to calculate 95% CIs and *p*-values.[17] The analyses will be adjusted for country, SMS-ICU (continuous variable 0–42), comorbidities (0, 1, 2 or +3) and ICU admission type (acute abdominal surgery, acute surgery other than abdominal or medical).

2.8 | Significance and interpretation

Two-sided *p*-values <.05 or 95% CIs, not including 1 for HRs or 0 for MDs, will be considered statistically significant. No corrections for multiple testing will be made, but we will describe all results as exploratory and cautiously interpreted, recognising the potential for type one errors.[18]

2.9 | Handling of missing data

We will contact local investigators for missing data. We will describe the extent of missing data for all variables. Descriptive data will be based on complete cases, and the proportion of missing data will be presented. In the Cox models, losses to follow-up will lead to censoring and thus not constitute missingness. If 5% or more of patients have missing data for one or more variables in a particular analysis, we will use multiple imputation with chained equations.[19] All outcomes, baseline variables listed above, and any use of prokinetic agents will be used in the imputation models. We will assume that data are missing at random and create 25 imputed datasets, and use predictive mean matching for continuous variables and logistic regression for categorical variables.[19,20] If multiple imputation is used, we will report analyses on the imputed data as the primary analyses. We will use complete case analysis for analysis if the number of patients with missing data for all included variables is less than 5%.[19]

2.10 | Administrative aspects

2.10.1 | Publication policy

We will submit the manuscript to an international peer-reviewed journal. All authors will declare any conflicts of interest. If any deviation from the protocol is necessary, it will be reported with explanations in the manuscript.

Funding sources will not influence data handling, analyses or manuscript writing.

2.11 | Authorship

Authorship will be granted to members of the Management Committee, as well as national and local investigators, according to the International Committee for Medical Journal Editors guidelines.[21]

3 | DISCUSSION

Prokinetic agents are recommended as part of the treatment of critically ill patients with delayed gastric emptying.[22] Still, the clinical relevance of this practice remains unclear, and data are ambiguous and heterogeneous.[5]

Epidemiological data on the use of prokinetic agents in the ICU are required to inform the planning of a randomised clinical trial.

The strengths of the described study include the planned international setup with expected high external validity, as well as the predefined protocol and statistical analyses. Furthermore, we will report the study according to the STROBE statement,[6] increasing the validity and transparency of the reported findings.

The study also holds some limitations. First, we have chosen to report only on four prokinetic agents in the ICU.[5] This could slightly underestimate their overall use, as some patients might be treated with other prokinetic agents. Second, we cannot be certain that all relevant risk factors associated with the use of prokinetic agents are captured in the study. Third, a risk of residual confounding exists in the analyses of the association between prokinetic agents and clinical outcomes. Finally, inherent methodological limitations include the risk of patients being lost to follow-up, incomplete data collection and missing data.[23]

4 | CONCLUSION

The outlined international cohort study will provide valuable epidemiological data on the use of prokinetic agents in adult, acutely admitted ICU patients.

AUTHOR CONTRIBUTIONS

Cepceptualisation and study design: VC, MHM, AP, WA, AG, LRK and MK. Writing first draft: VC, MHM, AG and MK. Critical review and approval of manuscript: all authors.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The Department of Intensive Care at Rigshospitalet—Copenhagen University Hospital (MHM, AP, AG) has received funding from the Novo Nordisk Foundation, and Sygeforsikringen "danmark" outside the submitted work. ARB has received speaker or consultancy fees from Nutricia and VIPUN Medical and is holding a grant from the Estonian Research Council (PRG1255). JH has received reimbursement for advisory board work (Paion) outside the submitted work.

DATA AVAILABILITY STATEMENT

No data is included in this study.

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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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