ISRCTN14399966 https://doi.org/10.1186/ISRCTN14399966

Esophageal motility disorders and gastroesophageal reflux in ventilated critically ill patients with different feeding tolerance: effect of prokinetics

Submission date
27/08/2020

Recruitment status
No longer recruiting

Registration date
03/09/2020

Overall study status
Completed

Last Edited
06/11/2023

Condition category
Digestive System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
High-resolution impedance manometry (HRIM) is the most modern method to measure motility (contractions) of the esophagus and its sphincters while also measuring impedance, which is able to detect the reflux (backflow) of fluid and gas from the stomach to the esophagus. However, esophageal functions in mechanically ventilated critically ill patients have not yet been studied using HRIM.

The study aims to characterize the key general features of esophageal motility functions using HRIM in mechanically ventilated critically ill patients. Second, to compare the pattern of abnormal esophageal physiology and gastroesophageal reflux in patients with low residual gastric volumes and high residual gastric volumes. Third, to evaluate the effects of metoclopramide and compare it to healthy controls. Finally, to determine the safety and feasibility of HRIM in critically ill patients.

Who can participate?
Participants in the study are critically ill adult patients and adult healthy volunteers as a control group.

What does the study involve?
Critically ill patients in need of respiratory support, who are recovering from the original insult and are already receiving full nutrition via a nasogastric tube (25 kcal / kg / day) and who also meet the inclusion criteria are classified into two arms: 1 / those who tolerate nutrition poorly, i. e. their regularly measured nutritional residues in the stomach exceed 500ml / 24 hours before inclusion in the study and 2 / those who tolerate nutrition well, i.e. residues not exceeding 100ml / 24 hours. On the day of the study, during sedation a manometric-impedance (HRIM) catheter is inserted along the nasogastric tube so that both the upper and lower esophageal sphincters and stomach cardia are visible in the recording window. After a 1-hour period of steady state, HRIM study data are collected for 5 hours together with detailed clinical and laboratory monitoring,

metoclopramide 10 mg is administered intravenously after the first 2 hours of measurements. In the control group, the HRIM catheter is inserted after 4 hours of fasting and first the esophageal functions are measured at rest. Then dynamic measurements are recorded upon swallowing 5 ml of saline (at least 7 valid swallows recorded). This is the fasting phase of measurements. After eating the study meal (250ml of nutrition drink) the postprandial phase is recorded, subsequently, metoclopramide 10 mg is administered intravenously and after a 5-minute pause the intervention phase is recorded. The study ends with extraction of the manometric catheter.
The only follow-up is ICU and hospital mortality. No drugs or invasive procedures out of the ordinary practice are used during this study.

What are the possible benefits and risks of participating?
In critically ill patients the obtained data can help optimize the treatment of the ongoing disease, or by adjusting the nutritional regime and its administration prevent the development of pneumonia, which can complicate mechanical ventilation. In control subjects, the standard manometric examination of the esophagus can detect possible axial hiatal hernia.

The potential risks include a discomfort resulting from nasal catheter insertion that will be addressed by administering a small dose of sedative or by catheter insertion in the early morning if sedatives are administered to induce night sleep. The catheter is thin and soft so any injury to the nose or nasopharynx during insertion is unlikely though it cannot be completely ruled out. The second potential risk is administering one dose of metoclopramide 10 mg intravenously. With the usual therapeutic doses of metoclopramide, side effects are rare and mild and transient. Fatigue, drowsiness, restlessness may occur frequently (approximately 10% of patients). Uncommonly, insomnia, headache, confusion, dizziness or mental depression, indigestion, urticaria and dry mouth may occur. Rarely (0.2% of patients), extrapyramidal side effects occur and, in most cases, manifest as acute dystonia. In practice, side effects are very rarely observed in critically ill patients.

All possible adverse events are registered, recorded and treated in accordance with the requirements of good clinical practice. Possible adverse events are reported to the State Institute for Drug Control in the standard manner. Each subject with a reported adverse event will be followed up and the progression of the adverse event will be monitored until it resolves, stabilizes, or is stated with certainty that it has no causal relationship to the study interventions. At the same time, any measures will be taken to resolve the adverse event according to the decision of the attending physician.

Where is the study run from?
Pilsen University Hospital (Czech Republic)

When is the study starting and how long is it expected to run for?
April 2012 to March 2016

Who is funding the study?
1. Ministry of Health (Czech Republic)
2. Charles University Research Fund (Czech Republic)
3. Ministry of Education, Youth and Sport of the Czech Republic (Czech Republic)

Who is the main contact?
Dr Karel Balihar
balihar@fnplzen.cz

Contact information

Type(s)
Scientific

Contact name
Dr Karel Balihar

ORCID ID
https://orcid.org/0000-0002-1940-983X

Contact details
1st Department of Internal Medicine
Faculty of Medicine in Pilsen
Pilsen University Hospital
Charles University Prague
Alej Svobody 80
Pilsen
Czech Republic
32300
+42 0720375344
balihar@fnplzen.cz

Type(s)
Public

Contact name
Dr Karel Balihar

ORCID ID
https://orcid.org/0000-0002-1940-983X

Contact details
1st Department of Internal Medicine
Faculty of Medicine in Pilsen
Pilsen University Hospital
Charles University Prague
Alej Svobody 80
Pilsen
Czech Republic
32300
+42 0720375344
balihar@fnplzen.cz

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Esophageal dysmotility and gastroesophageal reflux in adult ventilated critically ill patients with low and high residual gastric volumes and how it is affected by intravenously administered metoclopramide: a controlled, single center, prospective study using high resolution impedance manometry

Study objectives
1. Mechanically ventilated critically ill patients have impaired esophageal function compared to healthy subjects
2. The degree of esophageal dysfunction (motility, sphincter tone, reflux episodes) correlates with the degree of clinically determined upper gastrointestinal dysfunction (residual volume from nasogastric tube)
3. Metoclopramide improves lower esophageal sphincter tone and reduces the number of reflux episodes
4. Esophageal HRIM is safe and feasible in critically ill patients

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/06/2012, Local Ethical Committee at the Faculty Hospital in Pilsen (Edvarda Benese 13, 305 99, Pilsen, Czech Republic; +420 377 423 275; snebergerova@fnplzen.cz), ref: 230/2012

Study design
Explorative prospective single-center controlled comparative study with pharmacological intervention

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Esophageal dysmotility and gastroesophageal reflux in ventilated critically ill patients

Interventions
Critically ill hemodynamically stable patients fulfilling inclusion/exclusion criteria within 24-48 hours after reaching the enteral nutrition target of 25 kcal/kg/day are assigned according to residual gastric volumes to the low gastric volumes group (up to 100 mL/24h of gastric residual volume from nasogastric tube) or high gastric volumes group (more than 500 mL/24h). After calibration, high resolution impedance manometry (HRIM) catheter is inserted along the nasogastric tube so that both the upper and lower esophageal sphincters and stomach cardia

are visible in the recording window. After a 1-hour period of steady state, HRIM study data are collected for 5 hours together with detailed clinical and laboratory monitoring. Metoclopramide 10 mg i.v. is administered after the first 2 hours of measurements. There are no differences in the intervention in the low gastric volumes group and the high gastric volumes group.

Variables are measured during a 6 hour period on the day of the study, from 6 a.m. to 12 a.m. 6: 00 a.m. - 7:00 a.m. measurement of High resolution impedance manometry (HRIM) at steady state, 7:00 a.m. - 9:00 a.m. native HRIM, 9:00 a.m. - 12:00 a.m. HRIM after metoclopramide administration.

Control group subjects are healthy volunteers who agreed to participate in the study and fulfilled the inclusion and exclusion criteria. In the control group, the fasting phase HRIM is first recorded and analyzed according to Chicago classification version 3.0, then, after eating the study meal the postprandial phase is recorded and analyzed using the same protocol, subsequently metoclopramide 10 mg is administered intravenously and after a 5-minute pause the intervention phase is recorded.

The study ends with extraction of the manometric catheter. The only follow-up is ICU and hospital mortality in critically ill patients. No blinding or randomization is performed.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Metoclopramide

Primary outcome(s)
1. To characterize esophageal dysfunction in critically ill patients in comparison to physiologic conditions and to verify whether the administration of a prokinetic is effective in improving esophageal dysfunction in critically ill patients using:
1.1. High-resolution manometry (HRM) resting parameters of critically ill patients: tone of lower esophageal sphincter (mmHg); presence of hiatal hernia; inspiratory esophago-gastric junction (EGJ) pressure (mmHg); average maximal inspiratory EGJ pressure for three respiratory cycles; expiratory EGJ pressure (mmHg); average EGJ pressure midway between inspirations for the same three respiratory cycles; and esophago-gastric junction contractile integral (EGJ-CI) (mmHg. cm) measured in 3 periods in each study hour (10.-15., 25.-35. and 45.-55. mins) so that the landmark window is placed ideally in a quiescent portion of recording, free of swallows between 0 and 6 h
1.2. HRM dynamic parameters in critically ill patients: number of panesophageal activities/h; distal contractile integral (mmHg.cm.s); % of failed peristalsis; % of panesophageal pressurization; % of premature contractions; % of double peaked waves; % of triple peaked waves; distal latency (s); contractile front velocity (cm/s); integrated relaxing time (mmHg); and intrabolus pressure (mmHg) measured from all panesophageal activities at 0, 1, 2, 3, 4, 5, and 6 h
1.3. Both static HRM variables of tone of lower esophageal sphincter (mmHg), EGJ inspiratory pressure (mmHg), EGJ expiratory pressure (mmHg), and EGJ-CI (mmHg.cm); and dynamic HRM variables: distal contractile integral (mmHg.cm.s), distal latency (s), contractile front velocity (cm /s), integrated relaxing time (mmHg), intrabolus pressure (mmHg); in control patients measured in the fasting, postprandial and intervention phases, expressed as median of all values in each

phase
1.4 Impedance recording including:
1.4.1. The number of liquid, mixed, and gaseous reflux episodes (defined as a sequential oral progressive decrease/increase in impedance below/above 40% baseline values distally with a retrograde propagation by at least 2 additional proximal observed fields in the absence of explanatory peristaltic component (median/hour of study) between 0 and 6 h
1.4.2. The number (%) of distal and proximal refluxes between 0 and 6 h
1.4.3. The origin mechanism for each reflux episode: association with swallow or other esophageal activity (reflux within 10s of finished swallow), cough associated reflux (reflux within 30s of cough episode / interference with mechanical ventilation), absence of the LES tone (reflux at low LES tone below 5 mmHg, without an association with esophageal activity or cough), tLESR-reflux associated with a temporary decrease in LES tone below 5 mmHg, without association with esophageal activity or cough)
1.4.4. Esophageal activity, cough, agitation in the close post-reflux period (within 10s of reflux)
1.5. Clinical parameters of: mean arterial pressure, heart rate, respiratory rate, oxygen saturation, and body temperature using the mean from 3 values collected at 0, 1, 2, 3, 4, 5, and 6 h; intraabdominal pressure at 1.5 and 4.5 h; and ventilator setting (ventilator respiratory frequency, standard pressure and oxygen settings) at 0, 1, 2, 3, 4, 5, and 6 h
1.6. The dose of catecholamine, sufentanil and/or propofol use during study (%), the use of potentially interfering co-medication (such as beta-mimetics, beta-blockers, and parasympatholytics) are recorded between 0, 1, 2, 3, 4, 5, and 6 h
1.7. The time of oral and tracheal suction, cough or agitation, necessary manipulation with the patient and bolus drug delivery to nasogastric tube between 0, 1, 2, 3, 4, 5, and 6 h
1.8. Laboratory parameters of arterial lactate, hemoglobin, creatinine, bilirubin, albumin, C-reactive protein, international normalized ratio at 5:00 a.m., glycemia measured at 0, 3, and 6 h for critically ill patients and at 0 h for control patients
1.9. Demographic and outcome data of age, sex, and body mass index will be collected at the start of the study for all participants
2. To evaluate whether the most used clinical marker of upper gastrointestinal dysfunction in critically ill patients, i.e. residual gastric volume from nasogastric tube, correlates with the degree of esophageal dysfunction using both the parameters mentioned above and residual gastric volume from nasogastric tube measured at 1.5 and 4.5 h
3. Participant mortality will be measured using:
3.1. APACHE II score at time of admission and SOFA score on the day of the study will be collected for critically ill participants
3.2. Data on ICU and hospital mortality rate, number of ICU days, duration of hospitalization, and duration of mechanical ventilation will be collected for critically ill participants at the time of death or discharge

Key secondary outcome(s))

1. Feasibility and safety of performing HRIM in critically ill patients measured using the percentage of: cases of successful HRIM catheter insertion; and type of complications of insertion of HRIM catheter (such as epistaxis)
2. Statistical analysis measured using:
2.1. Data from the critically ill patients during the first 2 h of the study to analyze general features of esophageal motility functions in critically ill patients, and to compare the pattern of abnormal esophageal physiology and the occurrence of reflux in patients with LGV to HGV. When analyzing the data before and after metoclopramide administration in critically ill patients, data from the first 2 h of the study are evaluated against the following 3 h after metoclopramide.
2.2. Data from the control group during the fasting phase will be compared to the postprandial

phase and data from the postprandial phase with the data from the intervention phase
2.3. HRM data between the control group and critically ill patients will also be compared

Completion date
31/03/2016

Eligibility

Key inclusion criteria
Critically ill patients
1. Informed consent signed by a close relative and retrospectively by the patient when his/her condition allows it
2. Age of 18 years and above
3. Mechanically ventilated critically ill patient
4. Inclusion within 24-48 hours after reaching the enteral nutrition target of 25 kcal/kg/day
5. Maximum stable dose of noradrenaline up to 0.2 µg/kg/min
6. Enteral nutrition via nasogastric tube

Control group
1. Signed informed consent
2. Age of 18 years and above

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
16

Key exclusion criteria
Critically ill patients:
1. History of previous surgery on upper gastrointestinal tract
2. Gastroesophageal reflux disease
3. Portal hypertension
4. Active gastrointestinal bleeding
5. When an acute diagnostic or treatment procedure outside the intensive care unit at the time of HRIM measurements is required

6. Epilepsy, severe CNS damage or other contraindication for metoclopramide administration
7. Coagulopathy with INR value above 2.5 and platelets below 30x10e9/L
8. Pregnancy

Control group
1. History of previous surgery on upper gastrointestinal tract
2. Diagnosed gastroesophageal reflux disease or symptoms thereof, esophageal varices, or other organic esophageal or gastric disorder
3. Use of chronic medication, other acute or chronic illness
4. Pregnancy

Date of first enrolment
23/01/2013

Date of final enrolment
24/02/2016

Locations

Countries of recruitment
Czech Republic

Study participating centre
Pilsen University Hospital
1st Department of Internal Medicine
Faculty of Medicine in Pilsen
Charles University Prague
Alej Svobody 80
Pilsen
Czech Republic
304 60

Sponsor information

Organisation
Charles University Faculty of Medicine in Pilsen

ROR
https://ror.org/024d6js02

Funder(s)

Funder type
Government

Funder Name
Ministry of Health, Czech Republic - conceptual development of research organization (Faculty Hospital in Pilsen - FNPl, 00669806)

Funder Name
The Charles University Research Fund (project no.Q39)

Funder Name
Grant for “Fighting Infectious Diseases” awarded by the MEYS CR and financed by the EFRR project [CZ.02.1.01/0.0/0.0/16_019/0000787]

Results and Publications

Individual participant data (IPD) sharing plan
The data that support the findings of this study will be available from the corresponding author upon reasonable request (email: balihar@fnplzen.cz). Supporting data will be made available to Editorial Board Members and referees at the time of submission for the purposes of evaluating the manuscript and directly upon request to any reader on and after the publication date. Supporting datasets will be made available as Supplementary Information files that will be freely accessible on the journal´s website upon publication

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	08/02/2021	10/02/2021	Yes	No
Participant information sheet	Participant information sheet	05/09/2020	05/09/2020	No	Yes
Participant information sheet		05/09/2020	05/09/2020	No	Yes
Participant information sheet		11/11/2025	11/11/2025	No	Yes
Protocol file			06/11/2023	No	No