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Protocol Article

Nitroglycerin for oesophageal food impaction: protocol for a double-blind, randomised clinical trial

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ABSTRACT

INTRODUCTION. Oesophageal food impaction (EFI) is a common and potentially serious condition where a piece of food becomes lodged in the oesophagus. No significantly effective pharmacological treatment exists. Nitroglycerin (NTG) is a potent vasodilator that might induce sufficient smooth muscle relaxation to resolve the EFI. We aim to evaluate the efficacy and safety of NTG in EFI treatment.

METHODS. The study is an investigator-initiated, double-blind, multicentre, randomised, placebo-controlled, parallel-arm trial to assess the efficacy, safety and feasibility of NTG for patients with EFI. The study targets patients > 18 years of age with EFI. Patients will be randomised (1:1) to receive either oral NTG dissolved in 10 of ml tap water or oral placebo dissolved in 10 ml of tap water for up to two administrations separated by at least 30 minutes. The treatment resolves the food impaction if the patient can drink and eat afterwards.

CONCLUSION. The results of the study may guide future research and provide evidence for a pharmacological treatment option for oesophageal food impaction.

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Oesophageal food impaction (EFI) refers to a piece of food stuck in the oesophagus. It is relatively common, with an estimated annual incidence of 13 episodes per 100,000 persons [1]. Typical symptoms include sudden-onset dysphagia and chest pain during a meal. Total EFI prevents the swallowing of food, liquids and even saliva. The condition may resolve spontaneously, but can require pharmacological treatment or endoscopic removal under general anaesthesia. EFI should be treated within 24 hours, as prolonged EFI entails a risk of oesophageal perforation [2, 3].

Management strategies reported in the literature vary widely, including carbonated beverages, intravenous glucagon, calcium channel blockers, hyoscine butylbromide, diazepam and endoscopic procedures. No pharmacological option has demonstrated significant efficacy in randomised trials [4-6]. While endoscopic removal of EFI is effective, it is associated with a risk of oesophageal perforation, secondary mediastinitis and complications from general anaesthesia [7, 8]. Thus, a first-line pharmacological treatment is highly desirable.

In the North Zealand Hospital, Denmark, approximately 25% of EFI cases require endoscopic removal. For the remaining patients, food impaction either passes spontaneously or is treated on an empirical basis. All patients are offered a carbonated beverage, and some are prescribed diazepam.

Nitroglycerin (NTG) is a potent vasodilator widely used for acute ischaemic heart disease, acute heart failure and rapid relaxation of the uterus, with potential benefits in other conditions [9]. The time to onset of action for NTG is immediate, and the duration of action is 10-30 minutes, with a plasma half-life of 1-3 minutes [10].

Case reports suggest a temporal association between oral NTG administration and EFI symptom relief, although data remain limited [11-14]. The proposed mechanism of action is that NTG-induced relaxation of smooth muscles can resolve EFI by alleviating constriction in the oesophagus caused by either a primary motility disorder or a secondary oesophageal spasm. We do not expect NTG to resolve EFI caused by structural pathologies.

This study aims to evaluate the effectiveness, safety and feasibility of NTG in treating EFI. We hypothesise that NTG will resolve EFI in 25% of intervention group participants compared to an estimated 2% spontaneous resolution in the control group. If effective, NTG may provide a safe, simple and inexpensive EFI treatment.

Methods

The study is an investigator-initiated, double-blind, multicentre, randomised, placebo-controlled, parallel-arm trial to assess the efficacy, safety and feasibility of NTG for patients with EFI. No evidence-based pharmacological treatment for EFI exists; therefore, it is appropriate to study its efficacy and safety in a placebo-controlled trial. The protocol is registered in and authorised by the European Union Clinical Trials Register, EU trial number: 2023-503983-17-00. Authorisation date 28 AUG 2023.

Primary endpoint

The number of patients with resolution of EFI without the need for endoscopic removal when treated with NTG, compared to the number of patients with EFI resolution when treated with a placebo.

Inclusion criteria

Age > 18 years and legally competent

Presentation consistent with EFI:

Clear history of acute-onset dysphagia during a meal

Symptoms of oesophageal obstruction

Informed consent

Exclusion criteria

Sharp foreign body in the oesophagus (e.g. chicken bone)

Known structural abnormality in the oesophagus

Systolic blood pressure < 100 mg

Contraindications to the use of NTG

Recent use of phosphodiesterase inhibitors

Unresolved cardiac disease

Circulatorily unstable patient

Known severe liver disease

Pregnancy or breastfeeding

Any other disease/condition judged by the investigator to merit exclusion

Recruitment, screening and informed consent

Patients presenting at the Emergency Department or the Department of Otorhinolaryngology at North Zealand Hospital and Zealand University Hospital with EFI from 10 June 2025, will be asked to participate. We aim to include 88 patients. The patients will receive written and oral information about the project and sign informed consent before enrolment. Patients will be recruited by an ear, nose and throat doctor. We will attempt to recruit patients as they arrive at the hospital, before any other treatment is given.

Randomisation and allocation concealment

Patients meeting the inclusion criteria will be randomised, provided they do not meet any exclusion criteria. All enrolled patients will be randomised (1:1) to either the intervention or the control group. The Capital Region Pharmacy will perform the randomisation process. The allocation sequence list will be unknown to the investigators to allow immediate and concealed allocation.

Blinding, packing and labelling

Blinding, packing and labelling of the intervention and placebo will be performed at the Capital

Region Pharmacy. The placebo cannot be distinguished from NTG, i.e. the tablets are identical in terms of shape, size and colour, and both are tasteless and odourless. Blinding will be achieved by filling duma containers with NTG or a placebo and randomising the containers. The tablets are dissolved in 10 ml of tap water in a coloured cup to ensure blinding regarding potential visible particles. The labels will contain all required information in accordance with the randomisation list.

Unblinding

The investigators have 24-hour/365-day access to instructions on how to unblind participants if an emergency related to this study occurs. Instructions are kept at the department, and investigators can unblind the participants immediately at any time in case of an emergency. If there are indications of the intervention being either beneficial or harmful, an interim analysis will be performed. If an effect is confirmed, the trial will be unblinded before planned.

Intervention and drug registration

The study drug administration will be documented in REDCap either concurrently with or immediately after giving the participant the drug, including details such as batch number, expiry date, participant number, date and time, compliance and information identifying the healthcare professionals treating patients. Previous studies have described 0.4 mg NTG. [12, 14] In Denmark, soluble NTG is available in 0.25 and 0.5 mg doses. We chose 0.5 mg as this falls closest to previous trials. Willenbring et al. gave three doses five minutes apart. We know that a drop in systolic blood pressure can be a temporary side effect of NTG and therefore consider it wise to allow more time between the two doses.

The intervention group will receive a 0.5 mg Nitroglycerin “DAK” sublingual tablet from Takeda Pharma dissolved in 10 ml of tap water. Up to two administrations will be given, each separated by at least 30 minutes and only if the exclusion criteria are still not present.

The control group will receive a placebo tablet produced by the Capital Region Pharmacy dissolved in 10 ml of tap water. Up to two administrations will be given, at a minimum 30-minute interval.

All participants will be offered a carbonated beverage as part of the intervention, reflecting current standard practice for conservative EFI management in Denmark. Carbonated beverages are considered safe, with no known side effects or interactions with either NTG or placebo. By including this non-pharmacological treatment in both groups, the study design will maintain its internal validity while improving its external validity by more closely reflecting real-world clinical conditions.

Ten to 15 minutes after each treatment, the participant will be offered a carbonated beverage, and if able to drink, they will be offered soft food. If the treatment resolves the food impaction, it will be categorised as successful.

If EFI persists, participants will be offered the local standard treatment, e.g. diazepam and endoscopic surgery.

Statistical analyses

We aim to show a clinically relevant difference in the efficacy of EFI treatment with NTG (intervention group) compared to placebo (control group). We assume that 25% of patients in the intervention group will achieve immediate resolution of EFI, and that 2% of patients in the control group will achieve immediate resolution of their food impaction. The estimate of 2% spontaneous resolution in the control group (n≈1 patient) assumes that roughly 75% of EFIs resolve on their own, considering that our trial evaluates the effect of the study medication within a relatively short period of 0.5 to 1.5 hours. With a significance level of 5% and an estimated power of 90%, we need 44 patients in each study arm. This means that the total number of patients included is 88 (44 in each group).

The results, being categorical, independent data from two groups (intervention and control), will be analysed using Fisher's exact test. A p-value of ≤ 0.05 is considered statistically significant.

The following summaries will be presented for all screened patients: Enrolment: the number of days recruiting, the number of patients screened, the number of patients recruited, the number of screened patients not recruited and the reason for non-recruitment.

A CONSORT flow diagram will be used to summarise the number of patients screened, randomised and included, along with the number of patients who discontinued the intervention and those who will be lost to follow-up.

For baseline characteristics, patients will be described with respect to age, sex, time since EFI debut and previous EFI, both overall and separately for the two randomised groups.

Risks and reporting of adverse events

NTG has been tested and proven safe in numerous randomised controlled trials in heart disease. Side effects, contraindications and cautions are listed in our reference document [10].

As previously noted, diazepam is occasionally used as part of conservative EFI treatment in Denmark. Although this practice lacks scientific backing, we recognise that it is part of standard care in some regions. We do not view administering NTG to participants as risky, nor do we consider delaying local standard treatment by about one hour to evaluate the effect of NTG as unsafe. This short delay is within a clinically acceptable timeframe and allows for evaluation of the trial medication without compromising patient safety.

All adverse events (AEs) occurring during the first hour of administration are recorded in REDCap. Serious AEs are monitored through medical records for 90 days after discharge.

Investigators will report any serious or suspected unexpected serious adverse reaction (SUSAR) to the principal investigator and sponsor within 24 hours. The sponsor will notify the Danish

Medicines Agency and Medical Research Ethics Committees within 15 days, or seven days for fatal/life-threatening events, with follow-up information on such events provided within eight days. Other unexpected serious adverse reactions (SARs) are reported within 15 days of awareness.

The sponsor will submit annual SAR reports and a development safety update report (DSUR) through the Clinical Trials Information System (CTIS). Ninety days after trial completion, the sponsor will notify the Danish Medicines Agency (LMST) and, within one year, submit trial results via the CTIS in accordance with the Danish Medicines Act (Section 89, Subsection 2, No. 4).

Handling of patient data, data sharing and extraction

Data collected will include age, sex, prior EFI episodes, symptom duration before intervention, food type causing impaction, number of interventions, surgery time and duration, hospitalisation length, serious adverse events, randomisation number, treatment response and side effects. Data will be confidential, accessible only to local doctors and designated investigators, and possibly inspected by the DKMA.

Data will be processed per the Data Protection Regulation and Data Protection Act and retained for 25 years after publication. Participants will be informed that the Danish Health and Medicines Authority, the Good Clinical Practice (GCP) unit and the sponsor may access the full medical records during the study for control and inspection.

Anonymised published data may be shared upon request for result verification or meta-analyses. Trial protocol and participant information may also be available upon request; inquiries should be directed to the corresponding author.

Publication

Results from the study will be disseminated at conferences, national meetings and through scientific papers in medical journals. Positive, negative and inconclusive results will be submitted to peer-reviewed journals. All publications will follow the Consolidated Standards of Reporting Trials (CONSORT) statement [15].

Remuneration and insurance

The participants will be covered by the Patient Compensation Association. They will not be offered any remuneration.

Ethical concerns

The trial will be conducted in compliance with the protocol, the Helsinki Declaration, the GCP guidelines and national laws. The patients will be invited to provide informed consent to participate in the study, which they can withdraw from at any time. We consider the benefits of our intervention to outweigh any potential risks. We do not consider a delay of other treatment options to be of any risk to the patient.

Monitoring

The trial will be conducted according to the GCP guidelines and monitored by the GCP Unit at the University of Copenhagen.

Trial registration: European Union Clinical Trials Register, EU trial number: 2023-503983-17-00. Authorisation date 28082023.

Discussion

This trial aims to evaluate the efficacy of NTG treatment for EFI. If we establish that it is an effective treatment option, we will recommend oral NTG as a pharmacological treatment for EFI that should be offered before surgical treatment. A key strength of the study is its randomised, placebo-controlled design, which allows for the isolated evaluation of the therapeutic effect of NTGs. To enhance the clinical relevance of the trial, we have included a carbonated beverage in both study arms. Although the effectiveness of carbonated beverages has not been established through controlled trials, their widespread use in Danish emergency departments warrants their inclusion to better reflect real-world practice. This supports the external validity of the study while maintaining a clear focus on detecting any additional benefit attributable to NTG.

Ultimately, this trial may contribute important evidence to inform future EFI treatment guidelines and potentially reduce the need for surgical intervention in a significant subset of patients.

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References can be found with the article at ugeskriftet.dk/dmj

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