Trial Protocol

A Pilot study to test benefits of drinking clear fluids until called to the operating room in adult surgical patients

[HYDRATE-Trial]

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1 GENERAL INFORMATION

1.1 Administrative Information

1.1.1 Responsible Parties

Sponsor	University Hospital Würzburg, Institution incorporated under public law, represented by the Medical Director Josef-Schneider-Straße 2, 97080 Würzburg, Germany Authorised representative of the sponsor: **Prof. Dr. med. Patrick Meybohm** University Hospital Würzburg, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Oberdürrbacher Str. 6, 97080 Würzburg, Germany Tel: +49 931 201-30001 E-Mail: meybohm_p@ukw.de
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1.1.2 Trial/Study Registration

The trial will be registered on clinicaltrials.gov before enrolment of the first site. Wherever words denoting a specific gender are used in this protocol, they are intended to apply equally to all persons without regard to gender.

1.2 Synopsis

Title	A pilot study to test benefits of drinking clear fluids until called to the operating room in adult surgical patients.
Short title	HYDRATE-Study
Indication	Patients ≥ 18 years of age undergoing surgery without an indication for rapid sequence induction.
Primary end point	Primary efficacy endpoint: • Patient thirst (No; Yes, moderate; Yes, severe) Endpoint will be measured prior to anaesthesia induction.

Secondary end points	Key secondary endpoints:
	We will pilot test the intervention to demonstrate its acceptability and feasibility and to identify target outcomes for further trials.
	
	Piloting for feasibility assessment:
	• Total number of protocol deviations per group
	  ○ Outcome assessment successfully blinded
	  ○ Real fluid fasting time is less than allocated fluid fasting time
	• Fluid fasting time

	Piloting for future power calculations: • Richmond Agitation Sedation Scale (RASS) • Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) • Headache • Vital signs (delta heart rate, delta blood pressure) • Cumulative Vasopressor dose within 15 min after anaesthesia induction • Blood glucose level • Number of attempts for placing a peripheral intravenous catheter • Postoperative nausea and vomiting (PONV) Safety Endpoints: • Unplanned intensive/intermediate care unit stay due to respiratory complications • Confirmed bronchopulmonary aspiration • Death within observation period
Trial design	The study is a prospective, single centre, outcome assessor blinded, controlled randomised clinical trial (RCT) with 3 arms.
Trial population	Inclusion criteria on the individual level: Patients ≥ 18 years of age scheduled for surgery under anaesthesia care (general anaesthesia, regional anaesthesia, combined anaesthesia or monitored anaesthesia care) with an ASA physical status classification I-III. Exclusion criteria: Absolute and relative indication for rapid sequence induction, dysphagia, renal replacement therapy, fluid restriction therapy, pregnancy, expected need for postoperative mechanical ventilation and prior enrolment in this trial.
Sample size	n = 174 (55 per group +5% drop-outs = 58 per group)
Study Procedures	Group 1 (control) - **Usual care:** Fasting instructions as given by anaesthesiologist according to national guidelines (6 h solid meal and thick liquids, 2 h clear fluids). Group 2 (intervention) - **Instructed guideline adherence:** As per “Usual care”. In addition, the operating room schedule is closely monitored and the patient will be visited to be supported and encouraged in drinking clear fluids freely until 2 h before the anticipated beginning of anaesthesia. Group 3 (intervention) - **Experimental intervention:** As per “instructed guideline adherence” with the difference that the patient will be educated and encouraged to drink up to 200 ml clear fluids between 2 h prior to anaesthesia and the call to operation room. From this concludes that patients are allowed to drink up to 100 ml clear fluids every 1 h the anaesthesia is postponed. Follow-up per patient: 2 h after discharge from the operating room (up to 48 h e.g. in case of bronchopulmonary aspiration).
Biometry	Analyses will be intention-to-treat. The primary endpoint will be analysed by standard methods of descriptive statistics, namely chi-square test. The treatment effect will be quantified on the odds ratio scale with two-sided 95% confidence intervals provided. Secondarily, also point estimates and confidence intervals for the rate difference and the relative risk will be provided. The overall trial will have 80% power (alpha=0.05)

Trial Duration	**Duration of intervention:** On the day of scheduled surgery until call to the operating room. **Individual trial duration:** From the day of scheduled surgery until up to 2 h after discharge from the operating room. Follow-up might be postponed up to 48 h e.g. in case of bronchopulmonary aspiration. **Planned recruitment period:** 3 months The trial formally starts with the treatment of the first patient (FPI = first patient in), and the formal end of the study is the last follow-up visit of the last patient included (LPO = last patient out). The total study duration will be 3 months.

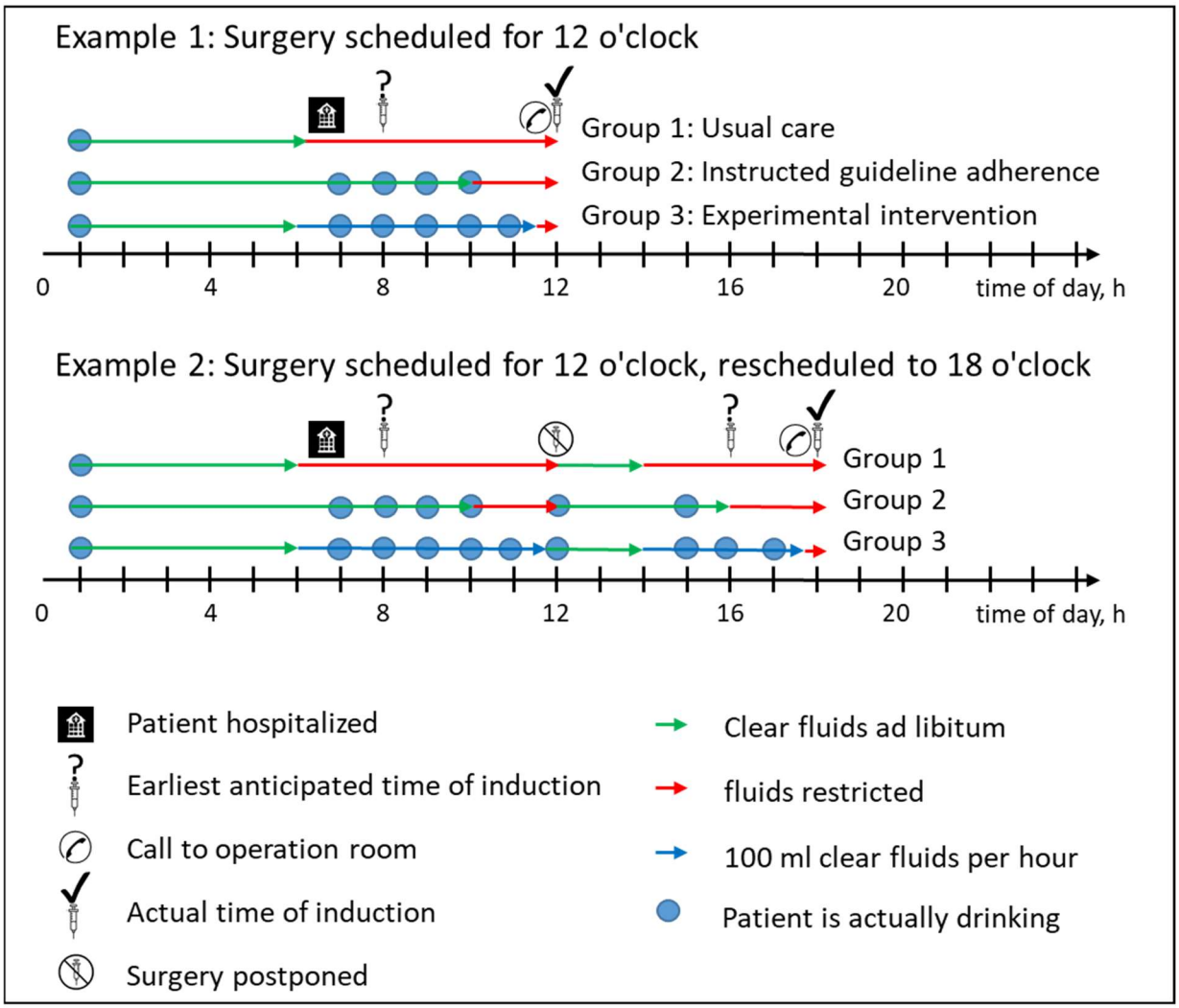


Fig. 1: Possible courses through the study

1.2.1 Schedule of Assessments and Procedures

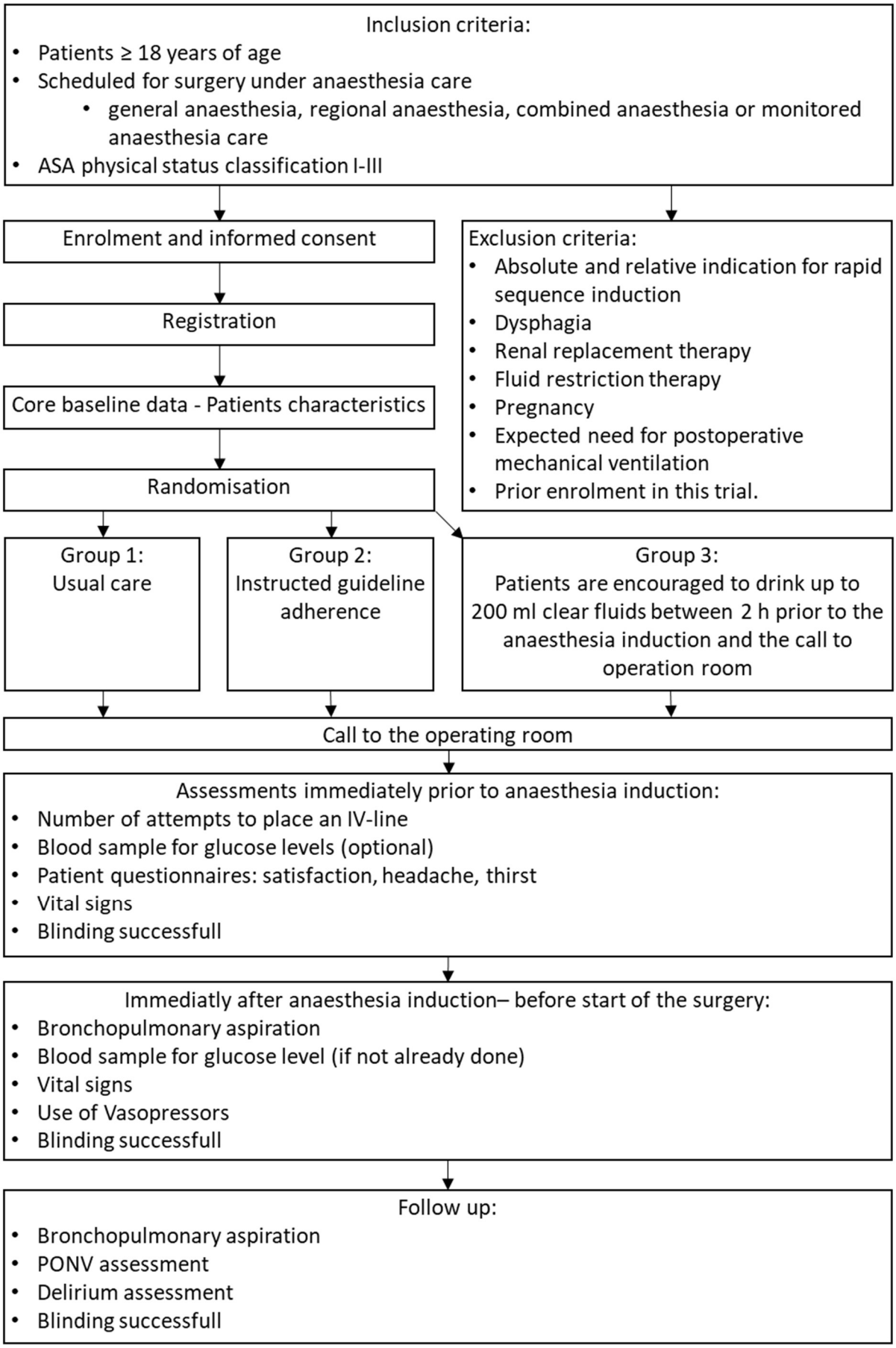
Examinations	Screening	Intervention	Prior to anaesthesia	After induction	Follow up
	28 days up to 0 days before surgery	On the day of surgery until call to the operating room	Immediately before anaesthesia induction	Immediately after anaesthesia induction	2 h (±30 min) after procedure[a]
Visit	V1	V2	V3	V4	V5
Inclusion criteria	X				
Exclusion criteria	X				
Informed consent	X				
Medical history[b]	X				
Baseline assessments	X				
Registration	X				
Demographics	X				
Randomisation	X				
Intervention		X			
Fasting time			(X)[c]		X
IV-catheter placement			X		
Patient satisfaction			X		X
Blood glucose level			X	(X)[d]	
Vital signs			X	X	
Use of vasopressors				X	
Bronchopulmonary aspiration				X	X
Headache			X		X
PONV					X
RASS + CAM-ICU					X
Blinding successful			X	X	X

[a]For general anaesthesia this is 2 h after extubation. For regional anaesthesia this is 2 h after skin suture. Parts of Follow up might be postponed up to 48 h e.g. if bronchopulmonary aspiration is to be confirmed.

[b]The premedication visit will be added to the study documentation to record the inclusion and exclusion criteria.

[c]Fluid fasting time must be greater than 30 minutes at anaesthesia induction. The actual fasting time will be assessed at the end of V5 to ensure outcome assessor blinding.[d]Only if not done at V4.

1.2.2 Study Flow Chart



2 INTRODUCTION

2.1 Medical Background

Preoperative fasting guidelines aim to minimize the risk of gastrointestinal regurgitation and bronchopulmonary aspiration with international guidelines recommending clear fluid intake up to 2 h and intake of solid foods and thick liquids up to 6 h prior to anaesthesia induction[1-4]. Perioperative bronchopulmonary aspiration events are rare[5,6] and full recovery is typical[6,7]. Even when fasting guidelines are not followed, perioperative bronchopulmonary aspiration rate has previously been reported as low as 0 % in low-risk populations such as patients undergoing ambulatory cataract surgery[8] or procedures other than endoscopy performed with procedural sedation[5].

Already three decades ago the adverse consequences of “Nil per os” (NPO) from midnight”-fasting practices have been recognized. Compelling research efforts demonstrating the benefit of allowing free clear fluid intake until 2-3 h preoperatively without increasing bronchopulmonary aspiration rates eventually resulted in changes to international guidelines[9,10,51]. While fasting guidelines have changed, extensive preoperative fasting remains common clinical reality[11-14]. Recently, new discussions have started debating further liberation of preoperative fluid intake restrictions in order to avoid dehydration and improve patient comfort[15-19].

2.1.1 Dehydration

Contradicting to “primum non nocere” the current practise may harm patients due to dehydration. Dehydration has been shown to worsen the outcome of strokes [20], raises the risk of infection, may prolong length of stay[21], lead to thrombosis, ACS[22,23] or acute kidney injury[24]. Dehydration aggravates pain in general and is discussed as a risk factor for post-lumbar puncture headache from iatrogenic spinal fluid leak [25].

Parenteral hydration may be considered as a solution, but the risk of infection increases with the time after IV-catheter insertion. Besides the typical risks and complications of an IV-catheter it also reduces patient mobility and contributes to patient stress. This contradicts modern treatment principles like Fast-Track. Furthermore, parenteral hydration does not alleviate dry mouth.
The first principle of 2017 NICE (National Institute of Health and Care Excellence) Recommendations is “Provide intravenous (IV) fluid therapy only for patients whose needs cannot be met by oral or enteral routes […]”. NICE further argues that a significant number of hospitalised patients were dying as a result of infusion of too much or too little fluid. [26]
According to NICE warning signs for dehydration include but are not limited to:

- systolic blood pressure is less than 100 mmHg
- heart rate is more than 90 beats per minute

2.1.2 Gastric contents

Over the last decade, point-of-care gastric ultrasound has advanced into a well-established and validated tool for evaluation of gastric content[27,28] in research as well as clinical settings. Gastric ultrasound may guide the assessment of bronchopulmonary aspiration risk and enable risk-adapted clinical decision making[29,30].
Preoperative fasting aims to reduce residual gastric volume and increase pH, because higher bronchopulmonary aspiration volume and acidity (e.g. pH < 2.5) are associated with higher mortality in animal models[31,32].
This is primarily of relevance for solid food, because drinking 200 ml water raises the gastric pH above pH 4 for a short period of time, as water not only dilutes gastric acid but also has a buffering capacity[33]. The time it takes for oral intake to move on from the stomach depends

largely on composition, calories and volume of the content. This is especially true if pathologies causing delay in gastric emptying are not present[34]. Half of ingested water volume is emptied from the stomach in about 10 min with complete clearance at around 40 min and 80% clearance at 30 min as demonstrated in various studies utilizing isotope activity, MRI imaging as well as gastric ultrasound to examine gastric emptying physiology[35-37].
Adherence to NPO does not automatically result in a completely empty stomach. A residual gastric volume of up to 1.8 ml/kg has been demonstrated among patients undergoing elective cholecystectomy and healthy volunteers[38,39]. In a study examining gastric emptying of water, there was no significant difference of emptying times or residual baseline gastric volume between individuals who remained NPO within 4 h prior to the experiment and those allowed water intake[40]. In accordance with the volume reported in a fasted state, a residual gastric volume above > 1.5 ml/kg has been proposed to indicate higher risk of perioperative bronchopulmonary aspiration[39].

2.1.3 Liberal fasting regime in paediatrics

Elaborate quality improvement initiatives in paediatric anaesthesia have been successful in their efforts to reduce fluid fasting among children[13,14,41], but fear of delay or cancellation of the procedure in case of fluid intake poses a substantial challenge. In some reports in the paediatric population, clear fluid intake was allowed until called to the operating room[42-44] without observing differences in bronchopulmonary aspiration events or cancellation/postponement of procedures[45]. Multiple renowned anaesthesia societies have issued statements endorsing more liberal oral fluid intake preoperatively in paediatric anaesthesia, like “6-4-1” or “6-4-0” fasting regimes[46-48].

Level of similar evidence in the adult population is low[12]. There is no plausible argument why adults should be different than children and teenagers in this matter. In fact, reported bronchopulmonary aspiration rates are higher among children[6]. Of note, recommendations of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine from 2005 permit adults to drink up to 150 ml and children up to 75 ml of clear fluids until 1 hour prior to anaesthesia[3].

2.2 Choice of Comparators

2.2.1 Hypothesis

We hypothesize that - compared to standard practice - allowing Patients ≥ 18 years of age undergoing surgery under anaesthesia care to drink clear fluids up to a volume of 200 ml between 2 h prior to anaesthesia and the call to operation room (approximately 30 min prior to anaesthesia induction) will decrease patient thirst and increase patient satisfaction.

2.2.2 Risk-Benefit Considerations

Besides the change in preoperative fluid intake, all patients will receive standard perioperative care.

Taking the available data into account it is unlikely for patients in the intervention group to have a substantially higher risk of bronchopulmonary aspiration or a different severity of bronchopulmonary aspiration complications.
Instead, they will be much less likely to experience excessive preoperative fasting durations, which may lead to preoperative dehydration and subsequently contribute to hypotension after anaesthesia induction[49,50]. This will furthermore improve patient discomfort characterized by increased hunger, thirst, anxiety, sadness, pain, stress and nausea[51-53] and may even positively influence early postoperative delirium[11] as well as the length of the hospital stay[54].

In paediatrics and labouring women[55] as well as for adults [51,56-58] allowing clear fluid intake until call to the operating room was already successfully implemented without an increase in bronchopulmonary aspirations being reported.

2.2.3 Significance

The growing practise of preoperative fluid consumption ad libitum needs a careful risk-benefit-consideration. It is therefore necessary to assess the benefits. This may pave the way to lift the burden of preoperative thirst from millions of patients yet to come, as the intervention is freely available und rapidly translatable into clinical practice.

2.3 Study objectives

2.3.1 Primary Objective

To evaluate if allowing patients to drink clear fluids until call to the operating room prior to anaesthesia induction will improve patient thirst compared to allowing clear fluid intake up to 2 h prior to anaesthesia induction.

2.3.2 Secondary Objective

We will pilot test the intervention to demonstrate its acceptability and feasibility - in particular we test if the outcome assessment is blindable. The secondary outcomes aim to identify targets for further trials.

2.4 Trial design

2.4.1 Trial Design

The study is an outcome assessor blinded randomised trial (RCT) with three parallel treatment arms.

3 METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES

3.1 Study Setting

The study will be conducted at the University Hospital Würzburg enrolling in- and outpatients.

3.2 Interventions

Group 1 (control) - Usual care: Fasting instructions as given by anaesthesiologist according to national guidelines (6 h solid meal and thick liquids, 2 h clear fluids).

Group 2 (intervention) - Instructed guideline adherence: As per “Usual care”. In addition, the patients will be visited to support and encourage them in drinking clear fluids freely until 2 h before the anticipated anaesthesia induction.

Group 3 (intervention) - Experimental intervention: As per “instructed guideline adherence” with the difference that patients are educated and encouraged to drink up to 200 ml clear fluids between 2 h prior to anaesthesia induction and the call to operation room. Education and information dissemination measures will be taken. Patients receive a container of known volume (e.g. cups, glasses, mugs, bottles with volume marks). From this concludes that patients are allowed to drink up to 100 ml clear fluids every 1 h anaesthesia induction is postponed. Patients may vary their fluid intake to meet this stipulation and their personal needs

e.g. by drinking 100 ml every hour or any other way that does not surpass 200 ml per 2 h (see Fig. 1).

3.2.1 Inclusion criteria

Patients may only be allowed to drink clear fluids up to call to operating room if they fulfill all the following criteria:

1. Adult patients (≥ 18 years)
2. Undergoing surgery under anaesthesia care: general anaesthesia, regional anaesthesia, combined anaesthesia or monitored anaesthesia care.
3. ASA physical status classification I-III

The proportion of patients undergoing general or combined anaesthesia is aimed to exceed 75%.

3.2.2 Exclusion Criteria

Individual patients may only be allowed to drink clear fluids up to call to operating room if they fulfill none of the following criteria:

1. Absolute indication for rapid sequence induction including but not limited to:
    a. Bowel obstruction including ileus
    b. Stricture and oesophageal disorders including achalasia
    c. Recent polytrauma or trauma of the upper gastrointestinal tract
    d. Acute abdomen/peritonitis including active gastrointestinal bleeding
2. Relative indication for (modified) rapid sequence induction includes, but is not limited to:
    a. Symptomatic gastroesophageal reflux disease, independent of food intake and persistent under medical treatment (PPI)
    b. Hiatus hernia or upside down stomach
    c. Upper gastrointestinal tumour
    d. History of upper gastrointestinal surgery (oesophageal, gastric, duodenum, pancreatic)
    e. Medically confirmed gastroparesis
    f. Severe obesity, defined as body mass index ≥ 40 kg/m^2
3. Dysphagia
4. Renal replacement therapy
5. Fluid restriction therapy
6. Pregnancy
7. Expected need for postoperative mechanical ventilation
8. Prior enrolment in this trial.

3.3 Adherence

3.3.1 Compliance

Physicians will retain the right to assign patients to a fasting regime as per national guideline and/or postpone anaesthesia induction if they are concerned for patient safety due to unforeseen risk factors for bronchopulmonary aspiration.

3.4 Concomitant Care

As shown by Rüggeberg et al.[56], allowing patients fluid intake until call to the operating room on its own does not reduce fasting times. Only if it is combined with encouraging the patients to drink the fasting time decreases signifficantly. We therefore estimate the effects of contamination bias to be small. To reduce the risk of timing bias the day-of-surgery-visit of the study staff to reencourage drinking is aimed to take place 2 h before anaesthesia is scheduled.

3.4.1 Overdose and Abuse

To ensure minimal risk of bronchopulmonary aspiration the attending anaesthesiologist retains the right to postpone anaesthesia induction, which is warranted in cases, where the patient exceeds the 200 ml fluids intake in the last 2 h or has consumed solid foods less than 6 h before anaesthesia induction.

3.5 Outcomes

3.5.1 Primary Outcome

The primary efficacy outcome is adapted from item #3 of the Bauer satisfaction questionnaire and measured prior to anaesthesia induction of anaesthesia: Have you had the following today: Thirst (No/ Yes, moderate/ Yes, severe)

3.5.2 Secondary Outcome

Piloting for feasibility assessment:

1. Total number of protocol deviations per group
    a. Outcome assessment successfully blinded
    b. Violation of fluid fasting time and fluid fasting time in general

Piloting for future power calculations:

2. Richmond Agitation Sedation Scale (RASS)
3. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
4. Headache
5. Vital signs (delta HF, delta RR)
6. Cumulative vasopressor dose within 15 min after anaesthesia induction
7. Blood glucose level
8. Number of attempts for placing a peripheral intravenous catheter
9. Postoperative nausea and vomiting (PONV)

Safety Endpoints:

10. Unplanned postoperative admission to an intermediate care unit (IMC) or intensive care unit (ICU) due to respiratory insufficiency.
11. Confirmed Bronchopulmonary aspiration
12. Death within observation period

3.5.3 Analysed population

See inclusion and exclusion criteria. Analysis is per intention to treat.

3.6 Participant Timeline and Individual Study Visits

Follow-up per patient: Until completion of the last Visit (regularly 2 h ± 30 min after procedure, up to 48 h after procedure if e.g. bronchopulmonary aspiration is suspected.)

Duration of intervention per patient: From randomisation until call to the operating room.

Informed Consent, inclusion and withdrawal from the study is handled according to ICH-GCP.

3.6.1 Visit 1: Enrolment in the Trial

Screening, registration and Randomisation (- 28 days up to -0 days before surgery):

Generally, the investigator or authorised qualified members of the study group in the trial site screen potential patients eligible for recruitment up to 28 days before surgery for general participation on the basis of pre-existing data (e.g., as available in medical records).

Registered patients will be randomised electronically using REDCap after enrolment: Qualified medical staff will gain limited access to the system using a personal password. Information to identify a participant uniquely and to confirm eligibility must be entered before the system will assign the randomised treatment allocation. Randomization will be automated by computer-assisted generation of random numbers, which will be transferred into a randomization decision and triggered web-based by qualified medical staff, so that allocation to the interventions is ensured (allocation concealment).

On the day of the surgery the patients fluid intake prior to anaesthesia will be noted on a worksheet. The respective worksheet will be handed out at enrolment to avoid recall bias. However, if the patient loses the worksheet, a new one is given to him. To ensure outcome assessor blinding the worksheet will be sealed in an envelope after the call to the operation room and until follow up is concluded.

3.6.2 Visit 2: Intervention

The intervention is described in detail in chapter 3.2.

3.6.3 Visit 3: Assessments prior to anaesthesia induction

To ensure safety, 30 min must have passed since call to the operation room and anaesthesia induction. The patient must also state that they have not drunk since being called to the operating room.

Anaesthesia induction in the sense of this protocol is defined as the beginning of the injection of the hypnotic for general anaesthesia and beginning of the injection of the local anaesthetic for local/regional anaesthesia.

- The primary efficacy outcome is measured immediately before anaesthesia induction of anaesthesia. Authorised medical staff use a modified Bauer satisfaction questionnaire to assess thirst.
- To assess secondary outcomes the questionnaire will include an item for headache.
- To assure the number of attempts for placing a peripheral intravenous catheter is documented correctly, each staff member involved in the anaesthesia of the patient is interviewed.
- Vital signs including heart rate and blood pressure will be collected from the routine data. The highest value 5 min prior to anaesthesia induction of anaesthesia will be documented.

- The blood sample for glucose levels might be drawn immediately prior to anaesthesia induction or immediately after anaesthesia induction (Values assessed within 15 min prior and 15 min after anaesthesia induction will be accepted).

3.6.4 Visit 4: Assessments immediately after anaesthesia induction

- If relevant bronchopulmonary aspiration is suspected, it needs to be confirmed by bronchoscopy or radiology imaging up to 48 h after anaesthesia procedure. In that case the patient will be monitored for an additional 48 h and the outcome will be documented in the eCRF and the AE/SAE section if applicable. The sponsor is to be informed of every instance of confirmed bronchopulmonary aspiration within 24 h even if the SAE criteria are not met. The risk/benefit consideration has to be revaluated.
- Vital signs including heart rate and blood pressure will be collected from the routine data. The lowest value 15 min after anaesthesia induction will be documented.
- If not already done, a blood sample for glucose levels is to be drawn.

3.6.5 Visit 5: Assessments at follow up (2 h ± 30 min after procedure)

Follow up takes place 2 h ± 30 min after the procedure. For general anaesthesia this is 2 h after extubation. For regional anaesthesia this is 2 h after skin suture.

CAM-ICU is a well validated[59-61] score that has been used in the awakening ward setting to detect immediate onset delirium[62]. As described in “CAM-ICU Training Manual and FAQ”, the CAM-ICU is not applicable if RASS[63] is -4 oder -5.
If CAM-ICU is negative, the Bauer satisfaction questionnaire will be obtained with all items and the item “Headache”.
If CAM-ICU is positive or indeterminable, the Bauer satisfaction questionnaire is considered indeterminable. Sicker patients being missing from the data might skew the data (Attrition-Bias).
An indeterminable Bauer satisfaction questionnaire will therefore be repeated on POD1.
PONV for up to 2 hours will be documented in the following dimensions: Vomiting, retching, nausea, and/or use of rescue medication.
The safety endpoints and feasibility assessments will be considered present if they occurred before the end of the last Visit.

3.6.6 Premature Termination of the Intervention Phase for Individual Patients

The trial intervention phase may be terminated prematurely in case of:

1. Eligibility criteria are not met.
2. At the judgement of the investigator for any other reason of medical prudence.
3. On request of the patient.

In case of premature termination of intervention phase, it is necessary to document the reason of termination and the current condition of the patient.

3.6.7 Plan for Further Treatment

Patients will be treated as usual after the individual treatment period of the clinical trial.

4 METHODS: ASSIGNMENT OF INTERVENTIONS

4.1 Allocation

Sequence Generation: Patients will be randomly assigned to either control or experimental group with a 1:1 allocation per computer generated randomisation schedule using permuted blocks of random sizes. The block sizes will not be disclosed.

Concealment Mechanism: Patients will be randomised using a web-based randomisation system (embedded in REDCap). Allocation concealment will be ensured.

4.2 Blinding

HYDRATE is a outcome assessor blinded trial, since the intervention is not blindable. The attending anaesthesist can be unblinded during the safety interview before anaesthesia induction. The endpoint assessment will be blinded.

If the safety interview is conducted in a way that unblinds the attenting anaesthesist (e.g. asking the patient if fluids were consumed in the past 2 h) measures must be taken to avoid unblinding the staff responsible for assessing the outcomes (e.g. conducting the safety interview while the staff assessing the outcome is not present in the room). If unblinding occurs the remaining visits should be conducted by blinded staff whenever feasable.

Unblinding of the staff conducting outcome assesment will be documented in the eCRF for visit 4-6 respectivly.

5 METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS

5.1 Data collection Methods

5.1.1 Case Report Form (CRF)

Data will be entered into an eCRF designed in REDCap by the Investigator or an authorised member of the study team.

5.2 Retention

As follow up ends before hospital-discharge, we do not expect relevant issues with retention.

5.3 Data Management

The information entered into the eCRF is systematically checked for completeness, consistency and plausibility by rules implemented in the EDC Tool such that discrepancies can be dealt with at data entry.

5.3.1 Archiving

All relevant trial documentation (Trial Master File) and the electronically stored data will be stored for at least 15 years by the sponsor after the trial's completion. At the trial sites, the investigators' files, patient identification lists, signed written consent forms, electronic copies of all eCRFs and the patients' files will be stored for at least 15 years after the trial's completion. If local rules or other legal requirements require longer periods of archiving, then these are to be met especially for the local patient files.

5.4 Endpoints

Endpoints are assessed as described in chapter 3.6.3-3.6.5

The primary efficacy outcome is thirst on an ordinary scale from 1 to 3.

With the assessment of this patient relevant endpoint prior to anaesthesia we keep the Statistical Description of the trial hypothesis.

5.4.1 Statistical Hypotheses/Statistical Estimation Method

H_0: Clear fluid intake until call to the operating room is not associated with reduced thirst at anaesthesia induction compared to restriction of clear fluid intake within 2 hours prior to anaesthesia induction on the Bauer satsifaction questionnaire item #3.

The primary endpoint will be analysed by chi-square test.

5.5 Sample Size

We plan randomising n=174 patients. n = 174 (55 per group +5% Dropout)

The primary endpoint of this study is thirst immediately before anaesthesia induction. For this purpose, the Bauer Satisfaction Questionnaire is dichotomised - "yes (moderate or strong)" vs. "no thirst". The three groups will be compared with each other. In the control group, based on Bauer et al, 2001, a value of 53% is assumed[64]. Based on our own experience it is assumed that the experimental intervention (group 3) has a relative effect of 50% and therefore only 26.5% of patients are still thirsty. For group 2 (Instructed guideline adherence) a somewhat weaker effect is assumed. We assume that thirst can be reduced to 30% in this group.

In order to detect these differences between all three groups using a Chi² test with a power of 80%, a total of 165 patients is needed - 55 patients per group.

Drop-outs

Assuming 5% drop-outs or non-informative patients we require 58 patients per group.

5.6 Statistical Methods

5.6.1 Analysis Population

The Full Analysis Set (FAS) will be as close as possible to the ideal implied by the intention-to-treat-principle.

5.6.2 Planned Methods for Analysis

Standard methods of descriptive statistics (e.g. chi-square test for the primary endpoint) will be used always indicating the number of valid and missing values. Summary statistic will be reasonably rounded to avoid pseudo-precision.

Demographic and other baseline parameters will be described for the whole FAS and by randomisation arm using standard methods appropriate to the scale.

Patients will be listed on whom no intervention or an intervention not corresponding to the randomisation arm was performed.

6 METHODS: HARMS/ ADVERSE EVENTS (AE/SAE)

The focus of this clinical trial is to find an appropriate fluid fasting strategy to optimize the risk-benefit ratio. HYDRATE investigates different fasting strategies concerning patient thirst.

Immediate safety of drinking fluid is not in the primary focus of the trial and generally considered safe.

Therefore, the collection, documentation and notification of safety relevant events are adapted for this clinical trial. Following data are of special interest:

- Data defined as **end points** (primary, secondary and safety).

6.1 Definition of (serious) adverse events

6.1.1 Adverse Events (AE)

Adverse events encompass any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease that arise newly or worsen after the beginning of the intervention.

6.1.2 Serious Adverse Events

An adverse event is defined to be serious if it

- **results in death**,
- **is life-threatening**,
- **requires in-patient hospitalization or prolongation of existing hospitalization**,
- **results in persistent or significant disability/incapacity**

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

6.2 Documentation of (serious) adverse events

Within this trial all variables defined as safety outcomes **meeting the definition of AE/SAE** will have to be reported to the Investigator in writing as soon as possible and documented on the eCRF. The eCRF has to be filled in shortly after each study visit.

6.3 Other Safety Relevant Issues

Other safety issues also qualify for expedited reporting where they might substantially alter the current benefit-risk assessment of an investigational intervention or would be sufficient to consider changes in the investigational intervention or in the overall conduct of the trial, for instance:

New events related to the conduct of a trial likely to affect the safety of subjects, such as:

- a serious adverse event which could be associated with the trial procedures, and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of intervention,
- a major safety finding from a newly completed preclinical study,
- a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational intervention in another country by the same sponsor.

6.4 Therapeutic Procedures

If a patient requires treatment as a result of an adverse event, then it must meet the recognised standards of medical care in order to restore the patient's health. Appropriate resuscitation devices and medication must be available in order to treat the patient as quickly as possible in the event of an emergency.

The actions taken to treat the AE/SAE must be documented by the investigator either in the appropriate CRF and/or using additional documents.

6.5 Dealing with Pregnancy

Pregnant and obstetric patients will not be enrolled in this trial.

7 ETHICS AND DISSEMINATION

7.1 GCP-Statement

All persons participating in the conduct of the trial (sponsor, authorised representative of the sponsor, investigators, etc.) commit themselves to observe the Declaration of Helsinki (Version Fortaleza 2013), [66] as well as all pertinent national laws and the current International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP).

7.2 Initial Submission

7.2.1 General considerations

General ethical considerations also include the consideration and compliance with the following standards, laws and provisions: Declaration of Helsinki, [66] EU Commission directive 2005/28/EC "Good clinical practice" (GCP), Proposal for Safeguarding Good Scientific Practice, and the EU Directive 95/46/EC (Data protection).

7.2.2 Submission to the Ethics Committee and Federal Authority

The protocol and all other associated documents will be submitted to the leading EC of the University Würzburg for appraisal. The trial can start only after obtaining a positive appraisal by the leading EC. All documentation regarding the submissions and their results must be filed in the Trial Master File (TMF).

7.3 Protocol Amendments

Changes made to the protocol that was appraised positively by the EC must be positively reappraised and approved if the changes

- are such that they may affect the subjects' safety, e.g. fundamental changes to the therapeutic procedures,
- result in further data collection that necessitates changes to the patient information and/or informed consent form,
- affect the interpretation of the scientific documents upon which the trial is based or the significance of the results of the trial,
- significantly affect the leadership or conduct of the trial.

In order to ensure most comparable conditions during trial conduct and in the interest of valid statistical analyses, the investigators or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases. Any amendment must be set out in writing, at the same time giving the reasons, and signed by all parties concerned. The amendment then becomes part of the study protocol and is to be filed in the TMF.

Amendments which might have an impact on the well-being of the subject (major amendments) such as the use of additional invasive procedures require an additional approval by the EC. In addition, a further informed consent form is to be signed by all trial subjects enrolled in the trial who might be affected by the amendment. In case of substantial changes new approvals of the leading EC are required before the changes become effective. Minor changes will only be submitted to the EC in a written form.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval opinion. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted to the investigator for agreement.

7.4 Data protection and Confidentiality

Within this study, personal data from the trial subjects incl. data regarding the therapy and the course of disease (medical results) will be collected locally at the trial site.

The data for the trial will be stored and processed in pseudonymised form (i.e. without reference to the patient's name) with the aid of an identification number. The patient's name will not appear on any case report form or in any other trial document submitted to the eCRF. All collected data will be kept confidential.

Data access is limited to authorised persons. Measures are taken to prevent loss of data and that the laws pertaining to data protection are observed. The data are protected from third party access and only members of the trial are permitted to have access. These members are sworn to secrecy.

In the event of withdrawal of consent, the necessity for storing data will be evaluated. Data not needed will be deleted immediately. Personal data will be stored in an anonymous manner after reaching the study aim/after finishing of all concomitant scientific projects 15 years at the latest, if there are no other regulatory or contractual time periods for archiving.

7.4.1 Declaration regarding Data Protection

During data entry, processing and analysis all requirements of the data protection act will be taken into account. Access to the data is strictly limited to authorised persons. Data are protected against unauthorised access.

7.4.2 Declaration regarding the Pseudonymised Transfer of Personal Data

The sponsor certifies herewith that the transfer of pseudonymised personal data will take place according to the documentation and communication regulations in §§ 12 und 13 of the GCP-guidelines.

7.4.3 Declaration regarding Data-Sharing

The data on which the primary publication of the HYDRATE trial results was based will be shared with interested scientists on request (e.g. for meta-analyses, health related registers or other scientific questions) if the sponsor agrees. Shared data will be anonymized. This offer extends for at least five years.

8 ADMINISTRATIVE AGREEMENTS

8.1 Adherence to the Protocol

The clinical trial described here will be conducted and analysed in accordance with local laws (GCP-Verordnung) and ICH guidelines for Good Clinical Practice (GCP).

Protocol violations are all deviations from the procedures outlined in this document.

After a patient has been enrolled, it is the investigator's responsibility to avoid protocol violation in order to obtain unbiased data for the trial. Major protocol violations will be reported to the investigator/sponsor as soon as possible. All protocol violations will be documented and discussed with the responsible biometrician before closing the data base and carrying out the statistical analysis.

The investigator must ensure that the recorded data are documented as per protocol. Minor variations are an inevitability but must be documented together with a justification.

Protocol violations are documented in the eCRF.

8.2 Funding and Insurance

Patients are insured at Newline Europe Versicherung AG, Köln.

The number of the insurance policy is: NEV084616A

Copies of both insurance policies and the insurance conditions will be filed in the investigators file. A copy of insurance conditions will be handed over to the patient during informed consent process.

8.3 Publication Policy and Registration

The HYDRATE-Trial shall be published under the lead of the investigator together with contributing partners in a peer-reviewed journal, irrespective of the trial results. The publication policy will follow the recommendations of Good Scientific Practice (GSP) of the Deutsche Forschungsgemeinschaft (DFG, http://www.dfg.de) and will meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org).

Prior to study start, the clinical trial will be registered in a public trial registry (ClinicalTrials.gov).

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10 APPENDIX

10.1 Classification of Adverse Events

10.1.1 Degree of seriousness

The degree of seriousness of an Adverse Events will be determined in accordance with the definitions in 7.3.1 and 7.3.2..

10.1.2 Assessment of Intensity

The assessment of the intensity accords with CTCAE V4.0[65]

Mild Adverse Event	• asymptomatic or mild symptoms; • clinical or diagnostic observations only; • intervention not indicated.
Moderate Adverse Event	• minimal, local or non-invasive intervention indicated; • limiting age-appropriate instrumental ADL*[1].
Severe Adverse Event	• medically significant but not immediately life-threatening; • hospitalization or prolongation of hospitalization indicated; • disabling; • limiting self care ADL**
Life-threatening Adverse Event	• Life-threatening consequences; • urgent intervention indicated
Death related to Adverse Event	

10.1.3 Determining the Causal Relationship

The investigator/the deputy or the authorised medical staff must assess whether or not the Adverse Event is causally related to the intervention. The following classification is to be used.

- Reasonable possibility
- No reasonable possibility

10.1.4 Expected/Unexpected

Adverse Events are unexpected if they are no safety outcomes or regurgitation.

10.1.5 Outcome of an Adverse Event

The outcome of an Adverse Event is classified as follows:

- recovered/resolved
- recovering/resolving
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

*Note: A patient's death is not in itself an event, but the consequence of one. The event that led to the patient's death must be documented completely.

[1] **Activities of Daily Living (ADL):**
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11 PROTOCOL SIGNATURES AND AGREEMENT

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Investigator:		
Dr. Tobias Eberhard Haas	24.06.2024	
	Date	Signature
Biometrician:		
Prof. Dr. Peter U. Heuschmann		
	Date	Signature

Protocol Agreement

Herewith I declare that I have read and understood the present protocol and agree to honour each part of it. I will ensure that all the patients enrolled in the trial by my site will be treated, observed and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product and their duties.

Date: _____

Signature of Investigator: _____

Affiliation/address (stamp): _____

_____

_____

_____