

Hemodynamic and biochemical effects of intravenous versus oral fluids in healthy volunteers – A protocol for a randomized crossover trial

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Abstract

Introduction

Intravenous fluid therapy is widely used to manage critically ill patients, addressing hypotension, hypovolemia, reduced urinary output etc. However, its effects on mean arterial pressure (MAP) and cardiac output (CO) are often short-lived. Oral fluid intake, a less invasive alternative, may produce more sustained effects, but evidence is limited.

Methods

This Phase 1, single-center, randomized controlled crossover trial will include 20 healthy participants. Each participant will receive 1 liter of tap water (8–10°C) for oral intake over 10 minutes or 1 liter of Ringer's lactate (22°C) intravenously at 100 mL/min. After a 24-hour washout period, participants will switch to the alternate intervention. The primary outcome is the change in MAP 30 minutes after the start of fluid administration. Secondary outcomes include changes in CO, systemic vascular resistance index, stroke volume, and serum catecholamine levels.

Discussion

This study aims to provide new insights into the hemodynamic and biochemical effects of fluid therapy in healthy adults. By comparing the sustained effects of oral and intravenous fluid treatment, the results could improve patient care by reducing hospital admissions and healthcare costs.

Trial Registration Number

2024-519656-85-00

Summary box

- Intravenous fluid therapy is a cornerstone in emergency medicine, but its hemodynamic effects are often short-lived. Oral fluid therapy has shown potential for more sustained effects, but evidence is limited.
- This study aims to provide insights into the hemodynamic and biochemical effects of oral versus intravenous fluid therapy in healthy adults
- Oral fluid therapy could reduce the need for intravenous treatment, decrease hospital admissions, and optimize healthcare resources while improving patient comfort.

Introduction

Intravenous fluid therapy is a cornerstone intervention in emergency medicine, perioperative care, and critical care settings (1). It is routinely administered to address hypovolemia, with the goal of improving organ perfusion by increasing blood pressure and cardiac output. Despite its widespread use, the hemodynamic effects of intravenous fluids are transient, often dissipating within one hour (2). This limitation raises questions about its long-term efficacy, particularly in non-critical settings. Furthermore,

many widespread practices of intravenous fluid therapy were established based on historical or theoretical reasons rather than evidence derived from clinical trials. Most studies have been conducted in operating rooms and critical care units, making it difficult to extrapolate results to emergency departments, prehospital settings, or outpatient care for elderly patients (3).

While intravenous fluid therapy is generally cost-efficient, the expense of administering fluids intravenously can be significant, especially when using solutions such as colloids (4). In contrast, oral fluid therapy is non-invasive, eliminates the risks associated with intravenous access, and may offer a more economical alternative. Recent data (5) suggest that the blood pressure increase induced by oral fluid replacement lasts four times as long compared to intravenous fluids in hypotensive patients. The mechanism behind this sustained effect may be a rapidly rising sympathetic activity, thereby increasing plasma norepinephrine levels (6). Otherwise, literature comparing oral and intravenous fluid therapy is scarce, limited mostly to pediatric patients and sport medicine (7, 8)

This issue is particularly relevant given recent recommendations by the Danish Commission for Sustainability in Healthcare, which emphasized reducing unnecessary treatments and promoting healthcare delivery outside the hospital when feasible (9). The 2023 healthcare reform plan from The Danish Ministry of Health further supports this shift, aiming to move care closer to patients' homes. For nursing home residents, receiving treatment at home often aligns with their preferences and avoids the physical and emotional stress of hospital admission (10). When treatment at home is equally safe and more cost-effective, it becomes both an ethical and economical choice.

This study aims to compare the physiological effects of oral versus intravenous fluid administration on blood pressure, hemodynamic parameters, as well as biochemical markers in healthy adults. We hypothesize that a 1000 ml fluid bolus given orally has a greater effect on blood pressure than when administered intravenously.

Objective

To evaluate the hemodynamic and biochemical effects of oral versus intravenous fluid therapy in healthy adults.

Methods

Design and Setting

This trial is designed as a single-center, randomized, controlled crossover study. The study will be conducted in the Emergency Department (ED) of the University Hospital of Southern Denmark Esbjerg.

This study protocol is designed in accordance to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (11).

Study population

Female and male subjects will be recruited from healthy volunteers among the student body of the University of Southern Denmark and University College of Southern Denmark. Subjects will be screened for underlying disease via standard medical history taking, physical examination as well as a 12-lead ECG. Participants will be instructed not to urinate 2 hours prior to start of each trial day. The following inclusion- and exclusion criteria will be used:

Inclusion criteria

- Age between 18–64

Exclusion criteria

- Pregnancy (validated through a certified urine pregnancy test)
- Body mass index > 35 kg/m²
- Any medication use, with exception of allergy medication and contraceptives.

Randomisation and concealment

Patients fulfilling all inclusion criteria, and no exclusions criteria, will be randomized in a 1:1 ratio using the randomization tool implemented in the REDCap database. The OPEN data manager generates the allocation sequence.

Blinding

Given the specific circumstances of intravenous and oral fluid administration, blinding of neither participants nor investigators is possible. The statistician providing the analysis will be blinded to the type of intervention.

Intervention

Participants will be randomized to receive either 1 liter of oral tap water (8–10°C) over 10 minutes, or 1 liter of Ringer's lactate (22°C) intravenously at a rate of 100 mL/min. After a minimum washout period of 24 hours, participants will switch to the alternate intervention. Participants will be seated during the intervention and observed for two hours after start of fluid administration.

Outcomes

- **Primary Outcome:** Changes in mean arterial pressure (MAP) at 30 minutes compared to baseline following fluid infusion or oral fluid intake. The outcome was chosen based on a previous study showing the maximum effect of fluid therapy at 30 minutes. (12)
- **Secondary Outcomes:** Time for MAP to return to baseline, changes in visual analogue scale for pain (VAS), and alterations in vital signs (heart rate, temperature, peripheral oxygen saturation, cardiac index, cardiac output, systemic vascular resistance index, and stroke volume). Changes in serum-adrenaline and serum-noradrenaline and biochemical signs of cellular stress.

Data Collection and Management

All data will be recorded by the research team and entered in the electronic database REDCap via OPEN at OUH. The data will be securely stored on Sharepoint to ensure confidentiality.

During the two-hour study period, blood pressure, heart rate, peripheral oxygen saturation and ear temperature will be measured every 15 minutes using standard monitoring (Intellivue, Phillips, Denmark). Participants' discomfort levels will be evaluated every 15 minutes using VAS labelled from zero (no discomfort) to 10 (maximal discomfort imaginable).

Cardiac output, systemic vascular resistance, stroke volume, blood pressure, and pulse rate will be recorded continuously via ClearSight monitoring (Edwards Lifesciences, Denmark), which is a non-invasive device using plethysmography and arterial waveform analysis via an inflatable cuff on the middle phalanx.

Blood samples will be collected at baseline, 30, 60 and 120 minutes, measuring serum levels of adrenaline, noradrenaline, protein, albumin, hemoglobin, sodium, osmolality and extracellular vesicles (markers of cellular stress) (13). Urine samples will be taken at baseline and at 120 minutes, measuring urine sodium, osmolality and extracellular vesicles.

Power calculation

We expect oral fluid therapy to increase MAP by 5 mmHg more than intravenous fluid therapy at 30 minutes. With a power of 80% and an alpha of 0.05, we will require 20 participants considering dependent test statistics.

Statistical Analysis Plan

Descriptive statistics will be used to summarize baseline characteristics. Paired t-tests and repeated-measures ANOVA will be employed to analyze primary and secondary outcomes. A p-value of < 0.05 will be considered statistically significant.

Consent and Withdrawal

Informed written consents will be obtained in accordance with the requirements of the Danish Human Research Ethics Committee and applicable legislation. Participants may withdraw from the study at any time and data collected up to the point of withdrawal will be retained and included in the analysis unless

the participant explicitly requests its removal. Participants who withdraw after fluid therapy has been initiated will be invited to complete an end-of-study stay to assess any ongoing effects or adverse events to the treatment.

Safety and adverse events

The investigators will follow all relevant Danish and EU regulations in regards to adverse event and reactions. While any event deemed relevant will be registered, we do not expect any to occur given the safety of both oral and intravenous fluid therapy in healthy adults.

Ethics

The study will adhere to the Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects (14). All sensitive personal data will be protected and processed in accordance with the General Data Protection Regulation (GDPR), the Danish Data Protection Legislation, and the Danish Health Act. The protocol will be submitted to the Danish Medicines Agency and the Danish Medical Research Ethics Committees via the European Clinical Trials Information System (CTIS) for approval. The study will also be listed in the Region of Southern Denmark's internal research registry and registered with OPEN at Odense University Hospital (OUH). Insurance coverage will be provided through the Danish Patient Compensation system.

Timeline

- November 2024: Submission of final protocol to CTIS
- February/March 2025: Study initiation
- April 2025: Completion of data collection
- June 2025: Data analysis
- End of 2025: Manuscript submission for peer-review publication

Dissemination

Trial results will be disseminated through publication in peer-reviewed scientific journal and public presentations. Data will also be uploaded to CTIS and other relevant registries.

Perspectives

The physiological data gathered in this trial will contribute to a better understanding of hemodynamics and homeostasis in healthy individuals, setting the stage for studies exploring oral rehydration in patients. Validating oral fluid bolus therapy as an effective alternative to intravenous administration could lead to less invasive treatments, improve patient comfort, and reduce healthcare costs, especially in the emergency and prehospital setting. Moreover, these insights may lead to future research on oral fluid therapy in populations with specific health conditions such as sepsis, pancreatitis or gastroenteritis. These findings could potentially help optimize the capacity of healthcare systems to address future

demographic challenges, as more patients might be managed in primary care or at home, depending on their needs and treatment options.

Declarations

The Danish National Ethics Committee approved the protocol.

Conflict of interest

None declared.

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Figures

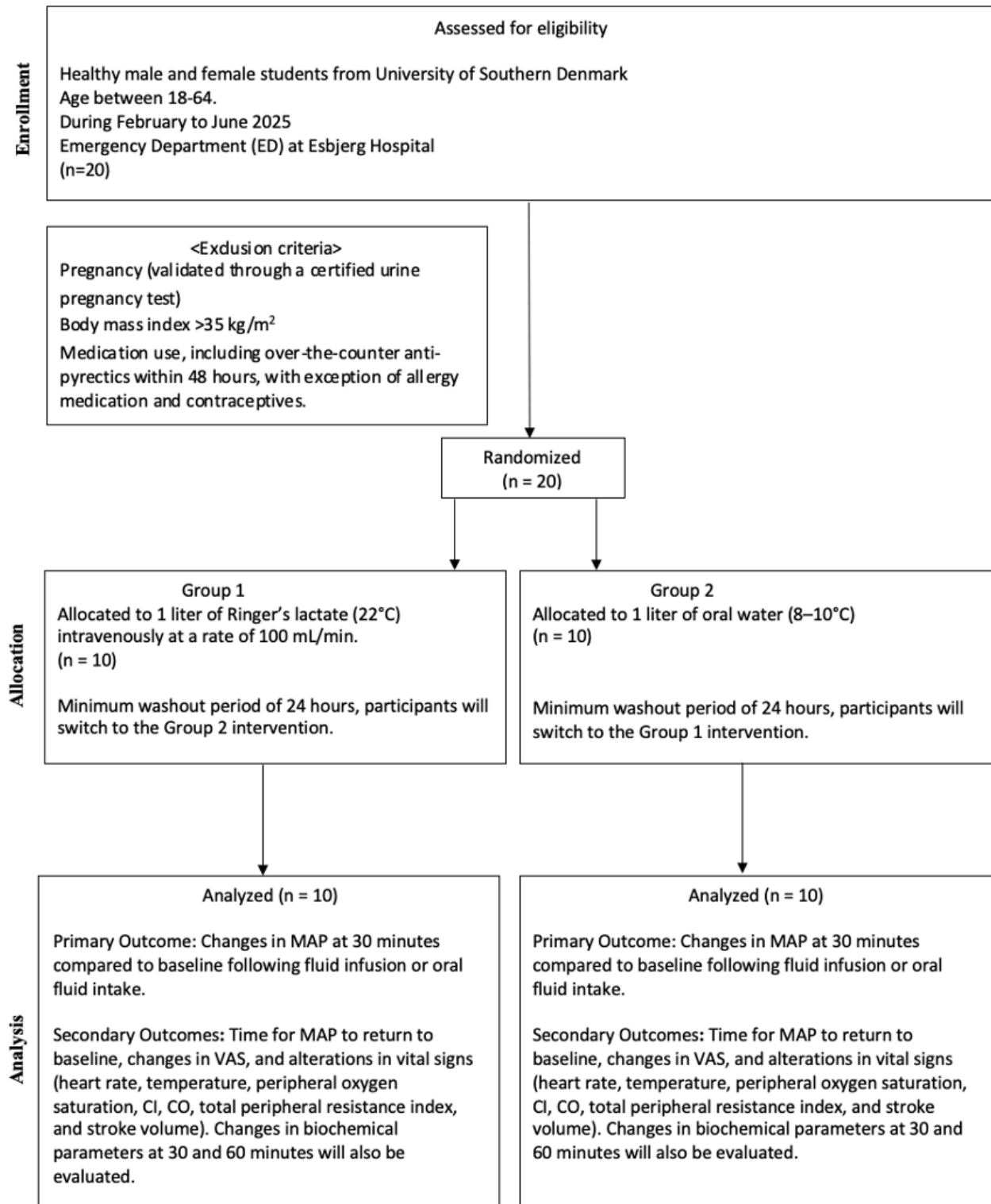


Figure 1

Consort diagram