# Subcutaneous Hydration in Geriatric Patients

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*DOI (link to publication from Publisher):*
10.54337/aau512910776

*Publication date:*
2021

*Document Version*
Publisher's PDF, also known as Version of record

This is a revision of the thesis where the citation to the now published papers the thesis is based on are included. All changes are marked with red.

# SUBCUTANEOUS HYDRATION IN GERIATRIC PATIENTS

by

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Dissertation submitted 2021

.

Thesis submitted: February 2021

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PhD Series: Faculty of Medicine, Aalborg University

ISSN:
ISBN:

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk



Printed in Denmark by Rosendahls, 2021

# ENGLISH SUMMARY


## Introduction

Dehydration is a common and potentially dangerous condition in older adults. When oral hydration is insufficient, patients are treated with parenteral hydration, where the common method is intravenous hydration. An alternative method is subcutaneous hydration, where a fluid is infused into the subcutaneous space from where it is absorbed into the bloodstream. However, the primary literature on the subject is conducted before the introduction of methodological guidelines. Furthermore, the physiology of subcutaneous infused fluid is only investigated in healthy older adults. With this PhD, we intended to create an updated overview and help fill some of the gaps in the available literature on subcutaneous hydration.

## Methods

We performed a systematic review, including critical evaluation and meta-analyses. Furthermore, we conducted an assessor-blinded randomized controlled trial (RCT) conforming to updated guidelines. We randomized patients to either intravenous or subcutaneous hydration, and observed patients for adverse effects, measured the time placing the catheters took, and examined the patients for signs of delirium. Finally, we investigated the absorption rate of subcutaneous hydration on frail older adults with comorbidities. Patients received a subcutaneous infusion containing a radioactive tracer. We measured the activity of the tracer and thereby calculated the rate and completion of absorption.

## Results

Based on data from our systematic review and our RCT, treatment with subcutaneous hydration causes fewer adverse effects than treatment with intravenous hydration (risk ratio 0.68, 95% CI 0.53 to 0.87). Furthermore, treatment with subcutaneous hydration results in fewer patients with agitation (risk ratio 0.41, 95% CI 0.23 to 0.73). However, subcutaneous hydration might be less effective at treating dehydration than intravenous hydration. The meta-analysis indicates that intravenous hydration lowers the serum osmolality by 3.49 mmol/kg (95% CI -0.72 to 7.7) more than subcutaneous hydration. The absorption of subcutaneous infused fluid is acceptable, with 88% of infused fluid absorbed one hour after the end of the infusion. However, around 10% of the infused fluid is left in a subcutaneous pocket with slower absorption.

## Discussion

There is a moderate level of evidence that subcutaneous hydration is safer than intravenous hydration in older adults. However, there is a low level of evidence that subcutaneous hydration might be less effective, with a reduced ability to lower serum

osmolality. In addition, a small portion of the infused fluid remaining in the subcutaneous space for a prolonged time. The reduced effect on hydration supports the recommendation that subcutaneous hydration is only relevant in patients with mild dehydration or impending dehydration. Our meta-analysis shows a considerable reduction in the risk of agitation when treating with subcutaneous hydration. However, the confidence in this estimate is low and deserves additional studies. Finally, it is much faster to place a subcutaneous catheter than an intravenous catheter. In conclusion, subcutaneous hydration deserves to be available wherever geriatric patients are treated; this is especially relevant in patients with difficult intravenous access or where personal is lacking the skill to place an intravenous access.

# DANSK RESUME


## Introduktion

Dehydrering er en hyppig og potentiel farlig tilstand hos ældre mennesker. Når oralt væskeindtag ikke er tilstrækkeligt, tilbydes patienter parenteral væskebehandling. Den mest almindelige metode er intravenøs væsketerapi, hvor væske gives direkte ind i blodbanen. En anden mindre kendt metode er subkutan væskebehandling, hvor væske gives som en infusion i underhuden, hvorfra den absorberes ind i blodbanen. De fleste primære studier er dog udført før indførsels af metodologiske retningslinjer. Herudover er fysiologien bag subkutan væskebehandling kun undersøgt på raske ældre. Med denne PhD afhandling ønsker vi at skabe et overblik over den kendte litteratur omhandlende subkutan væskebehandling og udfylde nogle af de huller der er.

## Metode

Vi har lavet et systematisk review med en kritisk vurdering og meta-analyser af litteraturen om subkutan væskebehandling. Herudover har vi udført et blindet randomiseret forsøg, hvor vi sammenligner subkutan med intravenøs væskebehandling. Patienter blev tilfældigt behandlet med enten intravenøs eller subkutan væskebehandling. Vi målte, hvor hurtigt nålene er at anlægge og observerede patienterne for bivirkninger og tilstedeværelsen af delir. Til sidst målte vi absorptionshastigheden, og hvor komplet absorptionen af subkutant infunderet væske er ved hjælp af en radioaktiv markør.

## Resultater

Baseret på data fra det systematiske review og vores eget randomiserede forsøg oplever patienter behandlet med subkutan væske færre bivirkninger end dem behandlet med intravenøs væske (relativ risiko 0.68, 95% CI 0.53 to 0.87). Ligeledes ses der færre tilfælde af delir hos patienter behandlet med subkutan væske (relativ risiko 0.41, 95% CI 0.23 to 0.73). Meta-analysen viser dog en tendens til, at intravenøs væskebehandling sænker serum osmolalitet med 3.49 mmol/kg (95% CI -0.72 to 7.7) mere en subkutan væskebehandling. Subkutan væske absorberes fint hos frail ældre patienter med 88% absorberet en time efter, at infusionen er indløbet. Dog efterlades ca. 10% af den infunderede væske i underhuden med en noget langsommere absorptionshastighed.

## Diskussion

Der er moderat grad af evidens for, at subkutan væskebehandling giver færre bivirkninger end intravenøs væskebehandling hos ældre patienter. Dog er der lav grad

af evidens for, at subkutan væskebehandling er dårligere til at sænke serum osmolalitet, og en lille del af den infunderede væske efterlades i underhuden med en noget langsommere absorptionshastighed. Den nok mindre effekt støtter anbefalingerne, at subkutan væskebehandling kun er relevant til patienter med beskeden grad af dehydrering eller til patienter i risiko for dehydrering. Vores meta-analyse viste at patienter behandlet med subkutan væskebehandling har en lavere risiko for delir. Dette resultat har dog kun en lav grad af evidens bag sig, og fortjener flere studier, der undersøger dette. Til sidst har vi fundet, at det er meget hurtigere at anlægge en subkutan væskeadgang end en intravenøs adgang. Vi konkluderer, at subkutan væskebehandling fortjener at være en tilgængelig metode, der hvor geriatriske patienter behandles. Dette er specielt relevant hos patienter, hvor intravenøs adgang er svært at opnå, eller hvor personalet mangler erfaring i at anlægge intravenøse adgange.

# ACKNOWLEDGEMENTS

I want to thank my main supervisor Stig Andersen, who started me on this journey and has helped me throughout with advice, guidance, and support. Without him, there would be no thesis. I would also like to extend my gratitude to my co-supervisors, Martin Jørgensen, for always being ready for a question or a friendly but heated discussion on methodology, Jesper Scott Karmisholt, for support, help with radioisotopes, and general feedback, and Jørn Munkhof Møller for aid recruiting patients. Furthermore, I would like to express my appreciation to my colleagues at the geriatric research department for their support, relevant discussions, and thoughtful questions that helped improve my research.

A special thanks goes to Gustav Valentin Gade for the help with graphical presentations in an area where I am hopelessly blind, Johannes Riis for his help in performing trials at any time with short notice without ever complaining, Elisa Worthington for the assistance in recruiting patients in the Emergency Department, Laura Marie Aalkjær Danielsen for her translation from French and proofreading of this thesis, and Lars Jødal for the aid in understanding nuclear medicine, without him the third study would be much less interesting or not at all.

I would also like to thank the all staff at The Department for Geriatric Medicine for your interest in my projects, the help in finding and observing patients for my projects, and the discussions on the clinical relevance of my results, the staff at the Department of Orthopaedic Surgery, Aalborg University Hospital, Department of Emergency Medicine, Aalborg University Hospital, and Akuttilbud Aalborg, Aalborg Kommune for the help in finding and observing patients for my RCT. Furthermore, I would like to thank The Department of Endocrinology and the Department of Nuclear Medicine Aalborg University Hospital for allowing me to use their equipment and the Unit of Clinical Biostatistics, Aalborg University Hospital, for the help selecting and performing statistical analyses.

Finally, I would like to offer my sincere gratitude to my wife, children, and extended family for their continued support, their love, and tolerance for my endless grumbles on the difficulties with recruiting geriatric patients.

Mathias Brix Danielsen
Aalborg, February 2021

# LIST OF PUBLICATIONS

This thesis is based on the following papers:

1. Danielsen M.B., Andersen S., Worthington E. and Jorgensen M.G. (2020), Harms and Benefits of Subcutaneous Hydration in Older Patients: Systematic Review and Meta-Analysis. J Am Geriatr Soc, 68: 2937-2946

2. Danielsen M.B., Worthington E., Karmisholt J.S., Møller M.M., Jorgensen M.G., Andersen S. Adverse Effects of Subcutaneous vs. Intravenous Hydration on Older Adults: An assessor-blinded RCT. *Submitted*

   It is the submitted version of the paper that is included in the thesis. The full citation of published paper:
   Danielsen, M. B., Worthington, E., Karmisholt, J. S., Møller, J. M., Jørgensen, M. G., & Andersen, S. (2022). Adverse effects of subcutaneous vs intravenous hydration in older adults: An assessor-blinded randomised controlled trial (RCT). Age and Ageing, 51(1). https://doi.org/10.1093/ageing/afab193

3. Danielsen M.B., Jødal L., Riis J., Karmisholt J.S., Valdórsson Ó., Jorgensen M.G., Andersen, S. Absorption Rate of Subcutaneously Infused Fluid in Ill Multimorbid Older Patients. *Submitted*

   It is the submitted version of the paper that is included in the thesis. Full citation of published paper:
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# ABBREVIATIONS

SC: Subcutaneous

IV: Intravenous

RCT: Randomised Controlled Trial

(e)GFR: (estimated)Glomerular Filtration Rate

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ROB 2: Cochranes Risk of Bias 2.0

CAM: Confusion Assessment Method

VAS: Visual analog score

CI: Confidence Interval

RR: Risk ratio

SD: Standard Deviation

MD: Mean Differences

SMD: Standardized Mean Differences

# CHAPTER 1. INTRODUCTION

Water is life

All living things depend on water, and it is difficult to imagine life without it.[1,2] Certainly, the human body could not function without, as it consists of 50-60% water, with the precise amount tightly regulated.[3–8] Unfortunately, inadequate hydration, also known as dehydration, is a common condition in older adults.[3,6,9–12] Since antiquity, it has been known that old age is associated with dehydration, as expressed by the Greek writer Homer, who suggested that old age is like a dried olive branch, and the philosopher Aristotle pointing out that "*One should know that living beings are moist and warm… However, old age is dry and cold*".[13]

## 1.1. BACKGROUND

Water is exceedingly vital in the human body and has a myriad of essential purposes.[5,8,14] One of water's most vital functions is its chemical properties. Water is both a solvent, a reaction medium, a reactant, and a reaction product.[13] Another essential function in the human body is the absorption of nutrients from the intestines. Water is secreted into the small intestines each day and then reabsorbed together with the nutrients. In both feces and as urine, water is a necessary component in eliminating the body's waste products. Water is also the central element in the transportation of nutrients, gases, and hormones around in our body as part of blood or intracellular fluid. Finally, water is essential in thermoregulation as sweat, in lubrication of joints as synovia, and as impact absorption in both joints and cerebral fluid.[5,8,14]

Water is part of almost all human processes, but water is essential even in the simplest forms of life. In NASA's search for extraterrestrial life, they are not searching for life but rather for signs of water. This conforms to the common belief that life cannot exist without water. However, recent discussions have questioned this statement, and although very interesting, this discussion is beyond the scope of this dissertation.[1]

### 1.1.1. THE REGULATION OF HYDRATION IS IMPAIRED WITH AGE

As previously mentioned, since antiquity, it has been known that older adults have an increased risk of dehydration, and there are multiple reasons for this. In principle, hydration is controlled by two factors: intake, primarily regulated by drinking water, and output, primarily regulated through urine production.
When the human body needs more fluid, a thirst signal is generated, and water is ingested. In humans, the thirst signal is primarily sent when the osmoreceptors sense

a relative hypertonicity or when the baroreceptors sense a reduced volume in the bloodstream. However, in older adults, the generation of the thirst signal is compromised.[15]

Studies have demonstrated that older adults drink less fluid than younger when exposed to a fluid restriction.[16] Furthermore, the infusion of hypertonic saline causing a hypertonicity that would generally lead to an increased fluid intake is also associated with less thirst in older adults.[17] Finally, both heat exposure and physical training where the participants were sweating were also associated with less thirst in older adults than in younger adults.[18–20] In older adults, neural imaging has shown less activity from both the centers in response to hypertonicity and hypovolemia, respectively.[13,15,20]

In younger adults, the portion of the body consisting of pure water is around 60%, while it is reduced to 50% in older adults. This reduction in total body water means that skipping drinks in older adults has a larger impact on the hydration status than in younger adults as a glass of water is a higher percentage of the total body water in the older than in the young.

The primary output for fluid is the generation of urine. The mechanism for controlling the output of fluid through the kidneys filtration is also compromised in older adults.[15] Increased age is associated with a reduction in glomerular filtration rate (GFR). It is shown that a younger adult can concentrate the urine up to 1100 - 1200 mmol/l compared to 400-500 mmol/l in an older adult.[15] This means that the older adult will continue to produce urine despite already being dehydrated.

### 1.1.2. THE RISK OF DEHYDRATION IN THE NON-HEALTHY OLDER ADULT

The mentioned changes with increasing age described above concern the healthy older adults; however, several common comorbidities further compromised the non-healthy older adult's hydration status. The simple task of getting water can be made difficult by reduced vision or arthritis. Another common comorbidity is sequelae from a previous stroke with either reduced mobility, cognitive function, or swallowing difficulties. These comorbidities potentially reduce the fluid intake of the older adult despite feeling thirst.[21] Furthermore, many older adults have a reduced bladder capacity. Some consciously reduce their fluid intake to avoid having to visit the bathroom often or reduce the risk of incontinence episodes. Finally, there is a common iatrogenic course for dehydration in the medical prescription of diuretics used to treat hypertension, cardiac failure, or peripherals edemas.[22]
The increased risk of dehydration is visible in data from both acute and non-acute settings. A study from Italy published in 2020 report that 52% of patients admitted from the emergency room to an internal medicine department were dehydrated or had impending dehydration.[6] In the non-acute setting of older adults in nursing homes, up

to 1/3 of patients are dehydrated or at risk of dehydration depending on the method of measuring and definition of dehydration.[23]

### 1.1.3. THE DANGERS OF DEHYDRATION IN THE OLDER ADULT

Dehydration is a potentially dangerous condition in older adults, and patients arriving at the acute assessment unit who are dehydrated have an increased risk of morbidity and mortality. However, it cannot be ruled out that the increased risk found is due to residual confounding.[3,6,12] Furthermore, with increasing levels of dehydration, there is an increasing impact on cognitive functions; with 1% of bodyweight missing as fluid, there is a mild reduction in cognitive function, and with a 5% loss, severe cognitive defects such as delirium can occur.[4,24]

### 1.1.4. DETERMINING HYDRATION STATUS IN THE OLDER ADULT

Is it challenging to diagnose dehydration or impending dehydration with objective clinical signs. Several standard methods such as skin turgor, capillary refill, urine volume, and others are of less diagnostic value. Other markers commonly associated with dehydration, such as orthostatic hypotension or electrolyte status, also have relatively poor diagnostic value, although they are better than the clinical signs.[25] However, the subject is challenging to investigate as there are no gold standards for hydration status.[4,26,27] Serum osmolality is often used as the reference standard; however, this marker only shows water-loss-only-dehydration.[28] Water and electrolytes loss dehydration is more challenging to determine. Missing drinks or a reduction of body weight over the last couple of days are reasonable indications of dehydration,[25] however, these are inaccessible in the acute assessment of hydration status.

### 1.1.5. ENSURING ADEQUATE HYDRATION IN OLDER ADULTS

The need for adequate hydration in older adults is a subject of some focus, and several methods have evolved to ensure this. Many older adults are aware of their reduced thirst feeling and have a bottle of water they need to empty twice a day to ensure adequate fluid intake. It is no longer their feeling of thirst that ensures sufficient intake but a cognitive process.[29] Furthermore, in older adults with cognitive impairment, personnel are aware and offer the older adults fluids often to ensure that they receive adequate hydration.[30] However, when oral hydration is insufficient parenteral hydration is necessary. In hospital settings, intravenous hydration is very common; however, the intravenous catheter requires training to place correctly. Subcutaneous hydration, where the catheter is placed into the subcutaneous adipose tissue of either the abdomen or thighs, is an alternative method that is surprisingly old. This method's first description is from the cholera epidemic in 1880[31] and used commonly until the 1950s. The invention of the plastic intravenous catheter made intravenous hydration

superior to subcutaneous hydration.[32,33] Several papers described severe adverse episodes with subcutaneous hydration possibly accelerated its demise.[34–36]
However, at the start of the 1980s, descriptions of its use in several hundred geriatric patients with very few severe adverse reactions were published.[37–39] These publications described the treatment of impending dehydration or mild dehydration. This contrasted with the older studies where severe adverse reactions were reported. [34–36] In these older trials, large volumes of fluid were infused in moderate to severely dehydrated patients with non-isotonic fluid. Since 1990, there has been an increasing interest and production of relevant scientific literature on subcutaneous hydration in the geriatric population and palliative care.[40–46]. Subcutaneous hydration is currently primarily used in geriatric medicine and some places in the primary sector, such as long-term care facilities. Several projects have described an interest in subcutaneous hydration and its potential for increased use.[47–49]

### 1.1.6. SHORTCOMINGS IN LITERATURE

We began working on the science for this PhD thesis when we tried to write a local guidance document on subcutaneous hydration, but we found limited updated literature. The most recent systematic review with a critical appraisal of the literature on the subject was published in 2007.[50] The included trials were published before the introduction of the methodological guidelines now required to follow when publishing in most journals.[50,51] An essential recommendation in these guidelines is the preregistering of trials. This practice reduces the risk of selective reporting bias where the reported outcomes are chosen if the result fits the author's narrative. Furthermore, items such as a flow diagram of patients, the reporting of how many patients each outcome is analyzed for, and the distinction between intention-to-treat and per-protocol analyses increase the publication's transparency. Finally, no trial on subcutaneous hydration has blinded outcomes assessors. Several studies have found an increased effect of an intervention in non-blinded trials compared to blinded trials when the outcome is a non-objective outcome.[52–54]

The physiology behind subcutaneous hydration has only been investigated in healthy older adults despite the method primarily being used on ill older adults.[55] As described above, the non-healthy older adult have several changes in their management of hydration status. With the difficulties in accurately assessing an older adult's hydration status, there is a need for understanding the physiology of subcutaneous infused fluid on the patients where it is used.

# CHAPTER 2. OBJECTIVES

This PhD's overall objective is to help fill some of the gaps in the literature on subcutaneous hydration. The goal is to qualify the writing of guidelines on hydration therapy, where the recommendations are based on sufficient evidence to meet any skepticism by physicians and nurses.

**Study I**
**Hypothesis I:** Subcutaneous hydration is a safe and relevant alternative to intravenous hydration.
**Aim I:** To perform an updated comprehensive systematic review of the available trials on the subject. Both to clarify where the literature on the subject is insufficient and create the basis for recommendations on the use of subcutaneous hydration in older adults.

**Study II**
**Hypothesis II:** Subcutaneous is as safe as intravenous hydration even in a high-quality assessor-blinded trial.
**Aim II:** To perform a randomized controlled trial (RCT) adhering to updated guidelines on RCTs to increase the strength of the recommendations on the use of subcutaneous hydration.

**Study III**
**Hypothesis III:** The absorption rate of subcutaneous infused fluid is acceptable in ill, frail older adults with comorbidities.
**Aim III:** To investigate subcutaneous hydration's physiology in the multimorbid, ill, older adult where it is used.

# CHAPTER 3. METHODS

This chapter includes the motivation for undertaking and the methods used in the three studies that form the basis for this PhD thesis. A detailed description of the methods used in each study can be found under the respective papers in the appendix.

## 3.1. SYSTEMATIC REVIEW – STUDY I

Title

Harms and Benefits of Subcutaneous Hydration in Older Patients: Systematic Review and Meta-analysis (Publish[56])

### 3.1.1. MOTIVATION

As described in the introduction section of this thesis, there is a need for an updated critical assessment of the known literature on subcutaneous hydration. We performed a systematic review that encompasses the search of all available literature on the subject and a critical evaluation of this. In our systematic review, we decided to focus on the risk of adverse effects with subcutaneous hydration as the potential harms of interventions are often overlooked in the scientific literature.[57] Furthermore, the risk of adverse effects was the primary concern when promoting subcutaneous hydration to other healthcare professionals. We were interested in investigating the risk of adverse effects when comparing subcutaneous with intravenous hydration and estimating the incidence and profile of adverse effects with subcutaneous hydration.

### 3.1.2. METHODS

It was essential for us to perform a high-quality systematic review as low-quality reviews can give misleading results. Our review is based on guidance from the Cochrane handbook[58], the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements with the harms extension,[57] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[59] Furthermore, we preregistered our protocol on PROSPERO: CRD42017071912 to reduce the risk of selective outcome reporting.

**Eligibility criteria**

All types of study designs were included in the review. There is the risk of selection bias when only including RCTs with the outcome of harms as the vulnerable patient

groups are often excluded in RCTs.[58] However, RCTs provide the best level of evidence when comparing interventions. Observational studies are excellent when investigating the incidence and profile of adverse effects as they avoid some of the selection bias in RCTs. Case reports are also relevant to include as they report on sporadic events unlikely to be found in other study designs. We knew from our preliminary searches that several articles on subcutaneous hydration were written in languages other than English. As such, we included papers written in any language.

**Information search and selection**

All relevant databases were searched from inception, and trial registries were searched for unpublished or ongoing RCTs. The risk of bias in RCTs was evaluated using Cochrane's Risk of Bias 2.0 (ROB 2)[60]. Observational studies were evaluated for the risk of bias by the criteria recommended by a GRADE.[61] The screening, selection of papers, data extraction, and evaluation of the risk of bias were performed independently by two researchers. Finally, we attempted to contact the authors of the included papers for any missing information on participants, outcomes, or risk of bias.

**Data synthesis and analysis**

For comparison between subcutaneous and intravenous hydration, we included only RCTs in the meta-analyses. To calculate the risk of adverse effects, we converted all data on adverse effects into adverse effects per infusion as we needed a relevant way of expressing "time at risk." The incidence of adverse effects was extracted from all included studies and only the studies with the lowest risk of bias to ensure a comprehensive presentation of the available information.

## 3.2. RANDOMIZED CONTROLLED TRIAL – STUDY II

Title

# Adverse effects of subcutaneous vs. intravenous hydration on older adults: An assessor-blinded RCT (Submitted) (now published[62])

### 3.2.1. MOTIVATION

A well-planned and conducted randomized controlled trial (RCT) has a low risk of bias and provides the highest level of evidence available from trials. The motivation for conducting a randomized controlled trial on subcutaneous versus intravenous hydration adhering to current guidelines was to corroborate previous research on the subject and increase the overall level of evidence on subcutaneous versus intravenous hydration. The trial's primary outcome was the risk of adverse effects as this is often under-prioritized in medical research[63] and as the concern for harms was a limiting factor in the use of subcutaneous hydration. We chose a non-inferior design for this trial as we did not expect nor needed to prove that there were fewer adverse effects with subcutaneous than with intravenous hydration. If subcutaneous hydration proved not to be worse than intravenous hydration, it would be a relevant alternative in patients where intravenous access is difficult to achieve. We used a non-inferior margin of 20%. We based this margin on a protocol for Cochrane review on achieving parenteral hydration and through discussion with consultants in geriatric medicine.[64]

### 3.2.2. METHODS

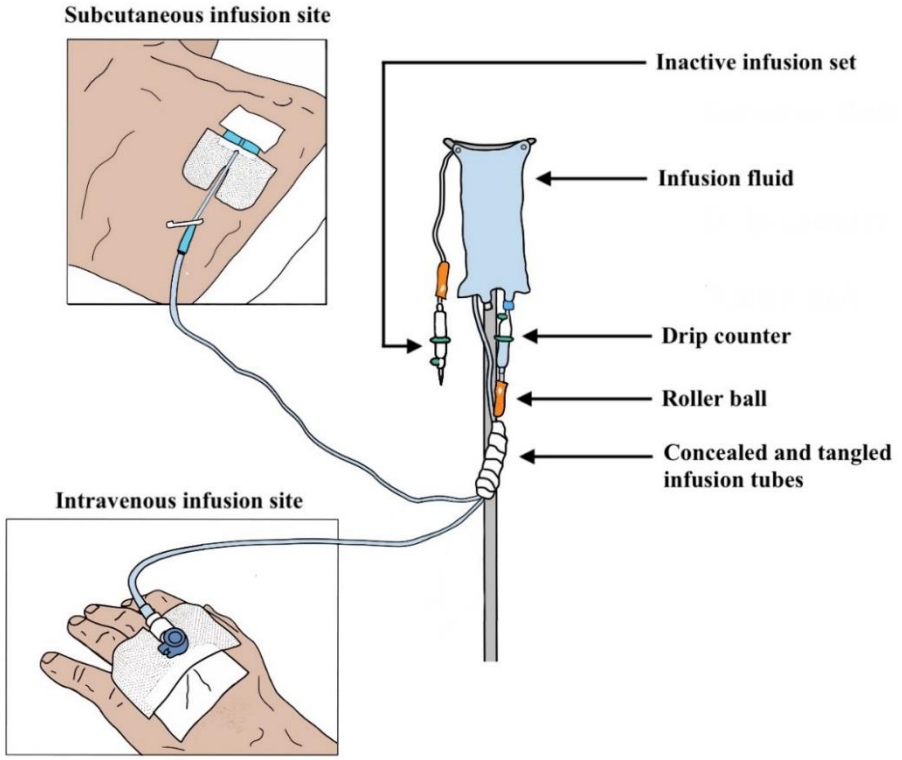
We performed a randomized controlled, parallel-group, assessor-blinded, non-inferiority trial. The trial was registered to clinicaltrials.gov NCT03710408 and follow the Consolidated Standards of Reporting Trials (CONSORT)[51] statement with the harms[63] and non-inferior extensions[65].

**Participants**
This trial's target participants were admitted older patients with mild dehydration or impending dehydration as it is this patient group where subcutaneous hydration is a suitable method. Eligibility criteria were: 65 years or older, admitted to the Emergency Room, the Orthopedic ward with hip fracture or Short-term care facility, need for 1-2 liters of fluid over the next 24 hours, and ability to provide informed consent.

**Intervention**
The patients were randomized to either intravenous or subcutaneous hydration and observed for adverse effects over 24 hours. We designed a trial setup where the outcome assessors for adverse effects would be blinded to the intervention as this has not previously been done in trials of subcutaneous hydration. Right after

randomization, the assigned catheter was placed according to local guidelines. However, before placing the dressing, a small square of fabric was placed over where the needle pierced the skin. We then removed the metal needle of the non-randomized catheter and placed the plastic catheter on top of the skin. The place where it should have pierced the skin was also first covered with a fabric square and then with the transparent dressing. Primed infusion lines were connected to both catheters, but only the one connected to the randomized catheter was inserted into a fluid bag. The infusion lines were tangled under the infusion bag, and this entanglement was covered with fabric. Figure 1 shows the trial setup. This setup blinded the outcome assessors as they could not determine which catheter was inserted correctly. However, they could still ensure that the infusion was running and change the infusion rate and even change the infusion bag if necessary. The outcome assessors reported observed adverse effects for both the randomized and non-randomized catheter.

**Figure 1.** Graphical representation of the trial setup. (Figure copied from Study II)




## Outcomes

Our primary outcome was the risk of adverse effects. We counted all discomforts experienced by the patient related to the infusion as adverse effects. This included

accidental removal of the catheter by the patient but not local edema at the infusion site if the patient could not feel it. Furthermore, we divided adverse effects into minor and serious (e.g., infection at the infusion site, pain requiring medication). We uploaded a complete description of what we included as an adverse effect before commencing the trial.

Of secondary outcomes, we studied the time it took to place the randomized catheter. We divided the time spend into six categories. The first four were different intervals in minutes, and the last two were requiring assistance from a colleague and requiring assistance from an intensive care nurse. Furthermore, we collected the patient's reported pain from the catheter's insertion and the patient's experience of the fluid therapy. These outcomes were collected on a VAS scale (0-100). Finally, patients were examined for delirium at the end of the trial using the Confusion Assessment Method (CAM)[66]. None of the secondary outcomes were blinded.

**Statistical analysis**

The statistical analysis plan was prepared in collaboration with a biostatistician and uploaded to clinicaltrials.gov before completing recruitment. Table 1 shows the statistical analysis plan as it was uploaded. For our primary outcome of adverse effects, we used a one-side z-test[67] as this is a non-inferior calculation. Furthermore, we would perform a superior analysis of our primary outcome if subcutaneous hydration was shown to be non-inferior to intravenous. Fisher's exact test was used for any dichotomous and ordered categorical data. A t-test was used for any outcome with discrete data. We planned not to perform any statistical analysis on dehydration markers as we run the risk of multiple comparisons and as these data can be challenging to interpret in patients with impending dehydration.

| Table 1 \| Statistical analysis plan | | | | | | |
|---|---|---|---|---|---|---|
| **Variable/outcome** | **Mode of assessing** | **Obtained by who** | **Variable type** | **Comment** | **Assumptions** | **Methods of analysis** |
| ***Primary outcome*** | | | | | | |
| Adverse effects (Blinded, non-inferior) | Visual inspection | Nurse | Dichotomous | | | z-test[a] (non-inferior) |
| **Further analysis of primary outcome** | | | | | | |
| Adverse effects (Blinded, superiority calculation) | Visual inspection | Nurse | Dichotomous | Only if non-inferiority is found | | One-sided Fisher's exact test |
| Adverse effects (total number, not blinded, non-inferior) | Visual inspection | Nurse | Discrete | | We expect non-normal distribution | Wilcoxon rans sum test (Non-inferior) |
| Adverse effects (total number, not blinded, superiority calculation) | Visual inspection | Nurse | Discrete | Only if non-inferiority is found | We expect non-normal distribution | Wilcoxon rans sum test |
| ***Secondary outcomes*** | | | | | | |
| **Clinical effects** | | | | | | |
| Death during hospitalization | Retrieved from patient chart | Data manager | Dichotomous | | | Fisher's exact test |
| Delirium | CAM-score | Nurse | Dichotomous | Comparing incidence of delirium at end of observation. | | Fisher's exact test |
| **Subjective evaluation** | | | | | | |
| Time spend on insertion | On a scale of 1-6[b] | Nurse | Ordered categorical | | | Fisher's exact test[c] |
| Discomfort during insertion (patient evaluated) | VAS (0-100 scale) | Nurse | Discrete | | | Wilcoxon rans sum test[d] Alternative t-test |
| Discomfort during infusion (patient evaluated) | VAS (0-100 scale) | Nurse | Discrete | | | Wilcoxon rans sum test[d] Alternative t-test |

**Table 1 continue**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Exploratory Objectives** | | | | | | |
| Risk of bleeding on patients prescribed anticoagulation medicine in SC group. | Visual inspection | Nurse | Dichotomous | Comparing patients with/without anticoagulation | | Fisher's exact test |
| Incidence rate of the different adverse effects on both IV and SC. | Visual inspection | Nurse | Discrete | Only to be examined visually in a box plot | | |
| **Descriptive Objectives** | | | | | | |
| Hydration markers[e] | Blood samples<br>BT | Laboratory technician, nurse | This data will be displayed as mean + sd at baseline, endpoint and change. Data not normally distributed will be displayed median and 25/75 percentile.[f] | | | |
| Charlson comorbidity index, Age, Sex | Retrieved from the patient chart | Data manager | Displayed as baseline values only | | | |

Copied from Statistical Analysis plan uploaded to https://clinicaltrials.gov/ct2/show/NCT03710408

a) This is the z-test for non-inferiority: $z = \frac{p_1 - p_2 - \pi}{\sigma}, \sigma = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$. Where $p_1$ is the proportion of patients experience an adverse effect in the SC group, $p_2$ is the proportion of patients experience an adverse effects in the SC group, and $\pi$ is the non-inferiority margin. With an alpha of 5%, we can reject $H_0$ if $z \geq 1.645$.

b) Nurses will estimate the time of insertion of the active infusion method into the following categories: 1: less than three minutes, 2: three to five minutes, 3: five to ten minutes, 4: ten to twenty minutes, If the primary nurse cannot achieve access, it will be noted if another ER nurse(5) or an anesthesiological nurse is needed (6).

c) We will combine rows (e.g., category 5 and 6 is combined into one) if there is a category with less than 1 observation or multiple with less than 5.

d) Previous studies on venous cannulation's discomfort found data to be non-normally distributed, even after log transformation.

e) The following parameters will be displayed albumin, creatinine, urea, osmolality, hemoglobin, sodium, potassium, blood pressure

f) We will refrain from performing statistical analysis on the effect of hydration. This is both due to the complexity of evaluating dehydration status on geriatric patients but also to avoid a type 1 error due to multiple comparisons.

## 3.3. SUBCUTANEOUS HYDRATION'S PHYSIOLOGY – STUDY III

Title

# Absorption Rate of Subcutaneously Infused Fluid in Ill Multimorbid Older Patients (Submitted) (now published[68])

### 3.3.1. MOTIVATION

A previous study has examined the absorption rate of a subcutaneous infused fluid. However, this was performed on healthy adults over 65 years.[55] Subcutaneous hydration is not used on healthy older adults but rather in the ill, frail, older adults with multiple comorbidities, and there is an increased leak from the capillaries in patients with acute illness.[69]

Furthermore, as described in the introduction section of this thesis, precisely determining the hydration status can be challenging. Consequently, examining the effect of hydration therapy can be tricky. Based on this, we found it relevant to perform a study examining the absorption rate of subcutaneous hydration on frail older adults with comorbidities.

### 3.3.2. METHODS

**Participants and study setup**

We recruited patients currently admitted to our geriatric ward if they were above 75 years and could provide informed consent. The patients received a subcutaneous infusion of isotonic saline wherein the radioactive tracer technetium-99m pertechnetate was mixed. This tracer emits gamma radiation that can be measured with a gamma detector. The previous study on subcutaneous infusion found that this tracer mimicked the flow of water in subcutaneous infusions.[55] To ensure the external validity, the infusions were set up as a continuous infusion. This is consistent with the standard method of subcutaneous hydration used in clinical practice. The included patients received an infusion of 235 mL of isotonic saline through a subcutaneous catheter placed in the abdomen's lower right quadrant. The initial infusion rate was 125 ml/hour. This was increased to 250 ml/hour after 10 minutes if the patients experienced no discomfort from the infusion.

**Measurements**

We measured the gamma activity at regular intervals from our tracer over the infusion site to estimate the absorption rate. Furthermore, to provide evidence that the infused fluid was absorbed into the bloodstream, we also extracted blood samples at regular intervals and examined the gamma activities in these. Finally, we measure the gamma activity over the thyroid gland as our tracer is accumulated here. The thyroid gland

activity could potentially be used as a marker for the absorption into the bloodstream in future studies.

### Statistical analyses

To calculate the amount of fluid gathered in the subcutaneous space, we calculated a patient-specific conversion factor enabling us to convert activity measurements into a volume of fluid. We used this conversion factor to estimate the amount of fluid at the end of the infusion and the rate at which this fluid was absorbed. Furthermore, we estimated the total amount of fluid absorbed, normalized our counts' data from both the blood and the thyroid gland to match this, and then calculated an absorption rate based on data from both the blood and the thyroid gland. Finally, we used regression analyses to estimate an absorption constant and half-life both from the subcutaneous space after the end of infusion and from the blood and the thyroid gland during the entire infusion.

## 3.4. UPDATED META-ANALYSES

### 3.4.1. METHODS

It would be relevant to update the meta-analyses from our systematic review with the data from our RCT. However, a risk of bias evaluation cannot be performed by us without a substantial risk of bias. As such, the meta-analyses presented here should be interpreted with caution, enhanced by the knowledge that the trial is not yet peer-reviewed. I have judged our RCT as low risk of bias in the outcome or adverse effects as this was the primary outcome of the trial, the outcome assessors were blinded, and the trial adhered to the other requirements of ROB 2. For the secondary outcomes, there are an insufficient number of trials for subgroup analyses based on the risk of bias to be relevant for interpreting the result, and these outcomes are more difficult to judge.

Our data from the RCT on the time of inserting the catheter is not measured in minutes but on a categorical scale and cannot be combined in a meta-analysis with the other studies in a meaningful way.

# CHAPTER 4. RESULTS

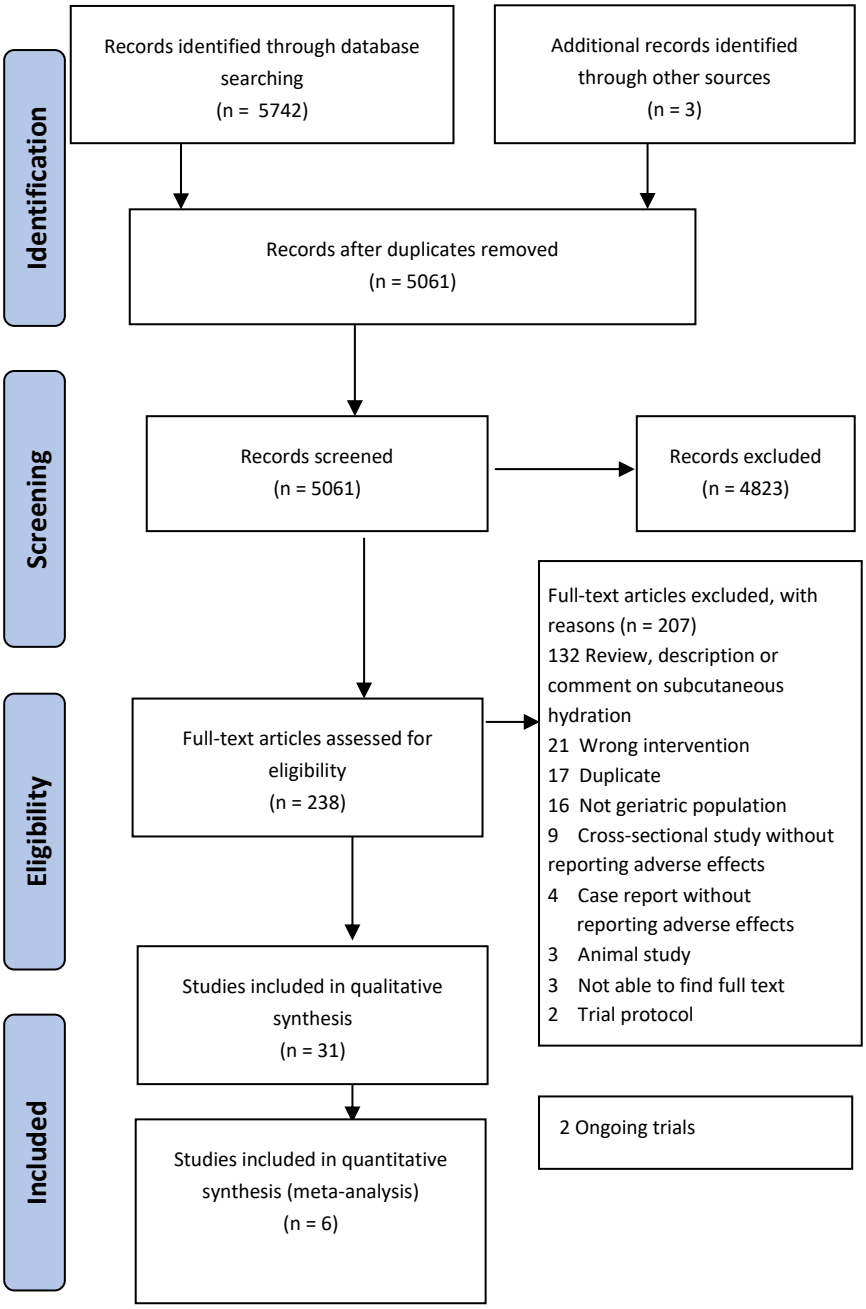
This chapter will describe the most relevant results from the three studies that form the basis of this thesis. A complete report of the results can be found under the respective papers in the appendix.

## 4.1. SYSTEMATIC REVIEW – STUDY I

**Study selection**

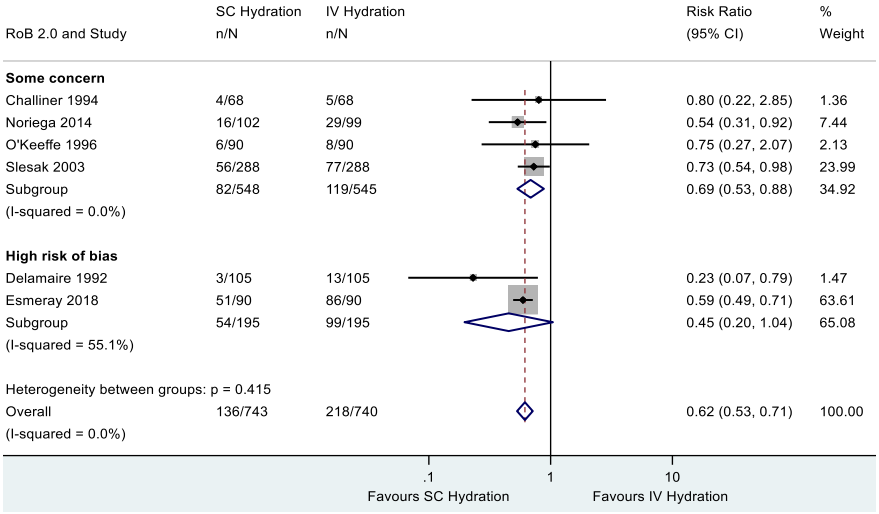
From our initial search, we found 5064 references, and we ended up with 31 publications on 29 studies after the screening process. See figure 2 for the selection process. The included studies were seven RCTs[41,42,46,70–73], one case-control trial[45], 11 prospective cohort studies[44,74–83], six retrospective cohort studies[40,43,84–89], and four case-control studies[90–93]. There were no RCTs with a low risk of bias. Four of the observational cohort studies had a low risk of bias.

**Figure 2. PRISMA flowchart**




Footnote: Figure copied from Study I, Danielsen et al. 2020

**Figure 3.** Meta-analysis of the number of adverse effects comparing subcutaneous hydration vs. intravenous hydration stratified by overall risk of



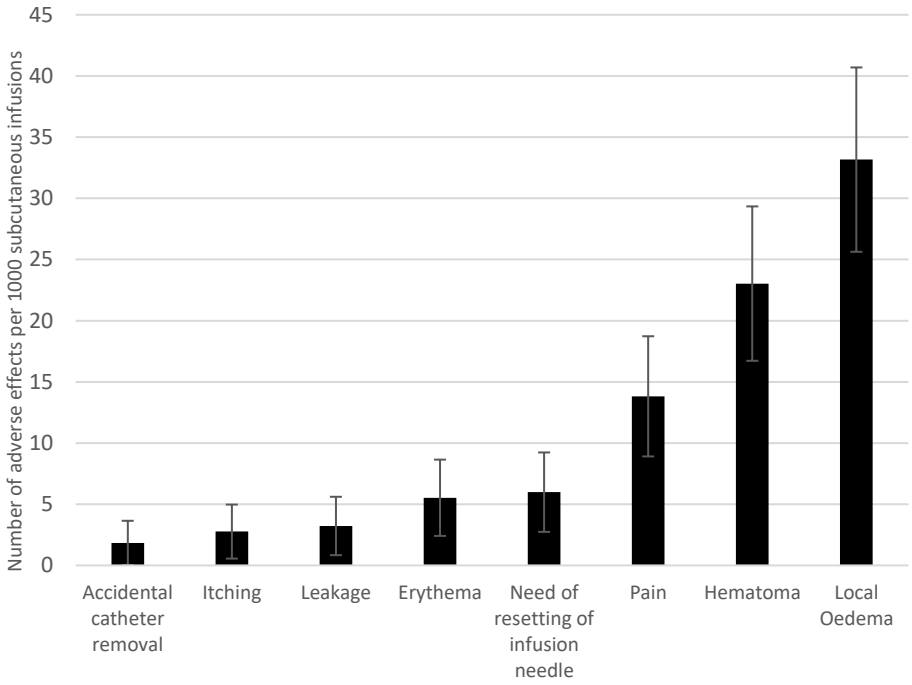

Footnote: Abbreviations: RoB 2.0: Cochrane Risk of Bias 2.0, n/N: Number of adverse effects/Number of infusions, CI: Confidence Interval, SC: Subcutaneous, IV: Intravenous.
Meta-analysis of pooled risk ratios using the random effects inverse-variance model with DerSimonian-Laird estimate of tau². The dashed line represents the overall pooled estimate. Figure copied from Study I, Danielsen et al. 2020

## Synthesis of results

Six of the seven RCT provided valid data on adverse effects. The meta-analysis on this outcome found a significantly lower risk of adverse effects with subcutaneous hydration than with intravenous (risk ratio 0.62, 95% CI 0.53 to 0.71, n=6). [41,42,46,70,71,73] When only the studies with the lowest risk of bias were included, the difference was a bit smaller but still significant (risk ratio 0.69, 95% CI 0.53 to 0.88, test for effect p=0.003, n=4, figure 3 and Table 2).

Combining data from the six RCT and the thirteen observational studies with extractable data[40–43,45,46,70,71,73,75–78,80,82,83,85–89] we found an incidence of adverse effects of 53 per 1000 infusion and when including only the studies with the lowest risk of bias, the incidence was 90 per 1000 infusion (95% CI 80 to 101, n=8).[41,42,45,46,73,76,80,82], Figure 4 shows the profile of the reported adverse effects.)

**Figure 4.** Incidence of minor adverse effects per 1000 infusions




Footnote: Data from the studies with the lowest risk of bias (in total n = 7, with 2171 infusions)[41,42,46,73,76,80,82]. I-bars represent the 95% confidence interval. One study reported data on serious adverse effects and the total number of minor adverse effects but not on specific minor adverse effects[45]. This caused the discrepancy between the number of included studies and infusions in figure 3 and the reported incidence of 90 per 1000 infusions. Figure copied from Study I, Danielsen et al. 2020

**Effect of subcutaneous rehydration**

As described in the introduction, it is difficult to measure the level of hydration precisely. As such, evaluating the effect of hydration treatment is difficult. However, meta-analyses showed a reduced effect of subcutaneous hydration in lowering serum osmolality, figure 5A and less fluid were infused with subcutaneous compared to intravenous hydration, figure 5B. Despite the results of a lower effect, there was a significant reduction in the risk of agitation, figure 5C. Finally, it was faster to insert the catheter for subcutaneous hydration than the catheter for intravenous hydration (figure 5D). A GRADE summary of findings for all outcomes can be found in table 2.

**Figure 5A.** Meta-analysis on the reduction of serum osmolality comparing subcutaneous vs. intravenous hydration using mean difference

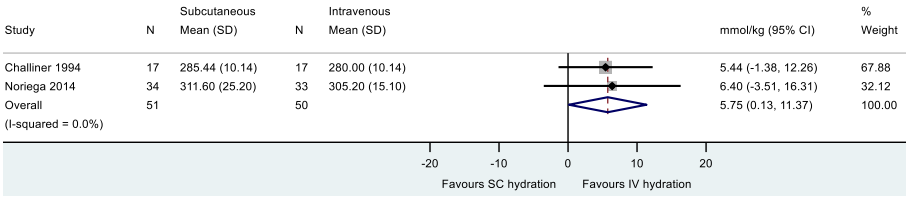



**Figure 5B.** Meta-analysis on the volume of fluid infused comparing subcutaneous vs. intravenous hydration using standardized mean differences

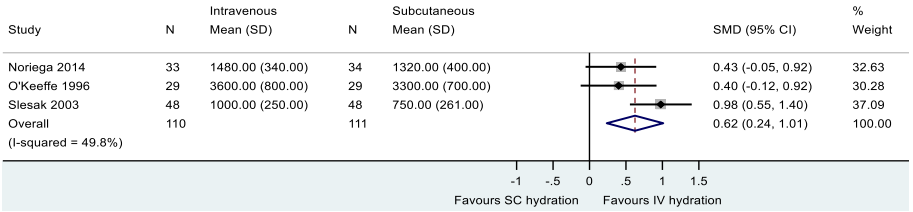



**Figure 5C.** Meta-analysis on agitation comparing subcutaneous vs. intravenous hydration using risk ratio

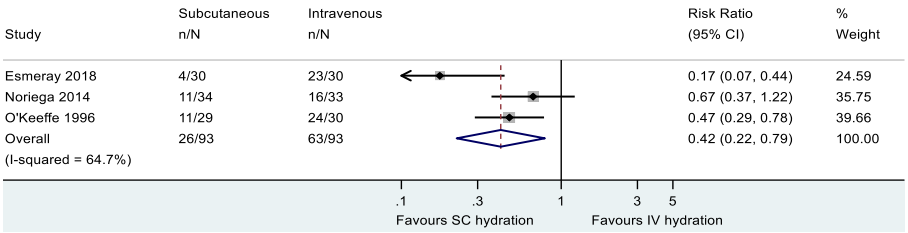
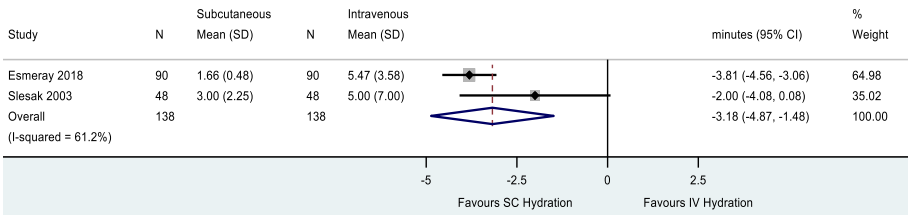



**Figure 5D.** Meta-analyses on time spend on catheter insertion comparing subcutaneous vs. intravenous hydration using mean difference




Footnote: Abbreviations: CI: Confidence Interval, N: number of patients, n: number of events, SD: standard deviation, SMD: standardized mean differences Meta-analyses of using the random effects inverse-variance model with DerSimonian-Laird estimate of tau². The dashed line represents the overall pooled estimate. Figures copied from Study I, supplementary, Danielsen et al. 2020

**Table 2.** GRADE Summary of findings: Subcutaneous hydration

| No of studies (design) | n/N of infusions SC | IV | Relative effect measure (95% CI) | Absolute effect | Quality of the evidence |
|---|---|---|---|---|---|
| **Risk of adverse effects** | | | | | |
| Subgroup with lowest risk of bias (4 RCTs) | 82/548 | 119/545 | RR 0.69 (0.53: 0.88) | The incidence of adverse effects with SC is **90** per 1000 infusions compared to **130** per 1000 infusions with IV (95% CI 102-169).[a] | ⊕⊕⊕O Moderate[b,c] |
| | n/N (SC) | n/N (IV) | | | |
| **Effect of treating the problem (dehydration), inferred from the surrogate outcome "Effect on s-osmolality"** | | | | | |
| (2 RCTs) | 51[f] | 50[f] | MD 5.75 (0.13: 11.37) | IV hydration lowers s-osmolality by **5.75** mmol/kg (95% CI 0.13-11.4) more than with SC hydration. | ⊕OOO Very low[b,c,d] |
| **Effect of hydration treatment, "Death"** | | | | | |
| (3 RCTs) | 3/84 | 2/82 | RR 1.26 (0.25: 6.34) | Meaningful absolute values unable to be calculated due to a very large confidence interval. | ⊕OOO Very low[c,d,e] |
| **Effect of the hydration treatment, inferred from the surrogate outcome "Volume of fluid infused"** | | | | | |
| (3 RCTs) | 110[f] | 111[f] | SMD: 0.62 (0.24: 1.01)[g] | IV hydration infuses **155** ml more fluid per day (95% CI 60 ml-253 ml) than SC hydration when infusing 1000 ml/day.[h] | ⊕OOO Very low[b,d] |
| **Effect of the hydration treatment, inferred from the surrogate outcome "Agitation"** | | | | | |
| (3 RCTs)[i] | 26/93 | 63/93 | RR 0.42 (0.22: 0.79) | **68%** patients treated with IV hydration with cognitive impairment experience agitation vs **28%** treated with SC hydration (95% CI 15%-54%). | ⊕⊕OO Low[b,d] |
| **Time spent on catheter insertion** | | | | | |
| (2 RCTs) | 138[f] | 138[f] | MD 3.2 (1.5: 4.9) | Setting up SC hydration takes **3.2** fewer minutes (1.5-4.9) than setting up IV hydration. | ⊕OOO Very low[b,e] |

Abbreviations: RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, CI: Confidence interval, RR: risk ratio, MD: Mean difference, SMD: Standardized Mean Difference.

[a] Based on incidence of adverse effects from SC hydration from the studies with the lowest risk of bias (4 RCTs and 4 observational studies.)

[b] Downgraded due to risk of bias of included studies

[c] Downgraded due to imprecision

[d] Downgraded due to indirectness

[e] Downgraded due to inconsistency

[f] Number of patients evaluated for this outcome

[g] We have use standard mean difference (SMD) as included studies reported either volume per day or volume overall.

[h] Based on numbers from Slesak 2003 with 1000 ml ± 250 being infused per day in IV group.

[i] All studies included mostly patients with cognitive impairment.

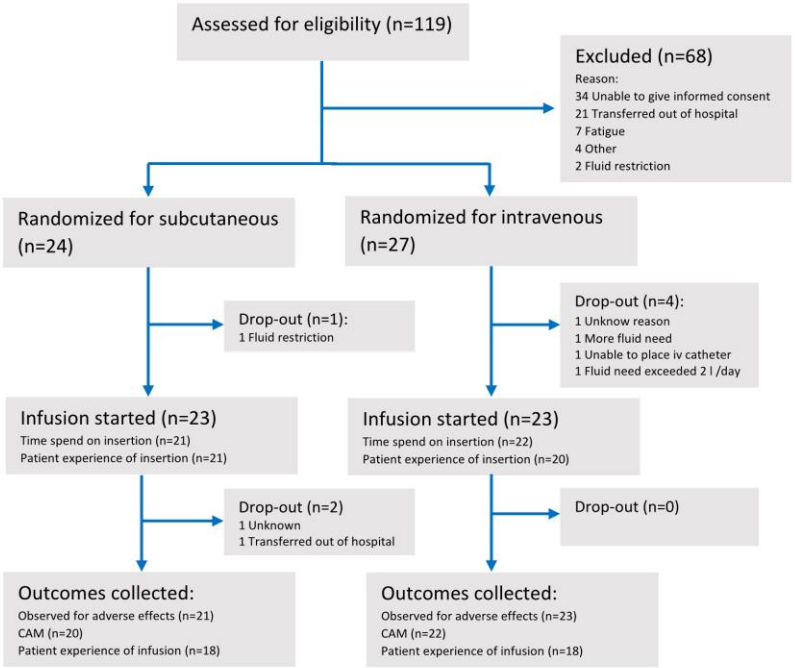
Table copied from Study I, Danielsen et al. 2020

## 4.1. RANDOMIZED CONTROLLED TRIAL – STUDY II

### Participants

We included 51 patients in total—twenty-four in the subcutaneous group and twenty-seven in the intravenous group. Patients had a mean age of 77 and 83 and a mean number of comorbidities of 4.7 and 3.9 in the subcutaneous and the intravenous group, respectively. See figure 6 for a flow diagram of included patients and table 3 for baseline information.

**Figure 6.** Flow diagram of patients




Abbreviations: CAM: Confusion Assessment Method[66], Figure copied from Study II

### Primary outcome

The trial was terminated before reaching our targeted sample size due to time limitations. Twenty-one patients in the subcutaneous group and twenty-three patients in the intravenous group were observed for adverse effects. Six (28%) patients in the subcutaneous group and ten (43%) patients in the intravenous group experienced at least one adverse effect. These numbers mean that subcutaneous hydration is non-inferior compared to intravenous for the outcome of adverse effects p=0.012, figure 7. However, subcutaneous hydration is not superior to intravenous with a non-significant risk ratio of 0.66 (95% CI 0.29 to 1.49, p=0.36.)

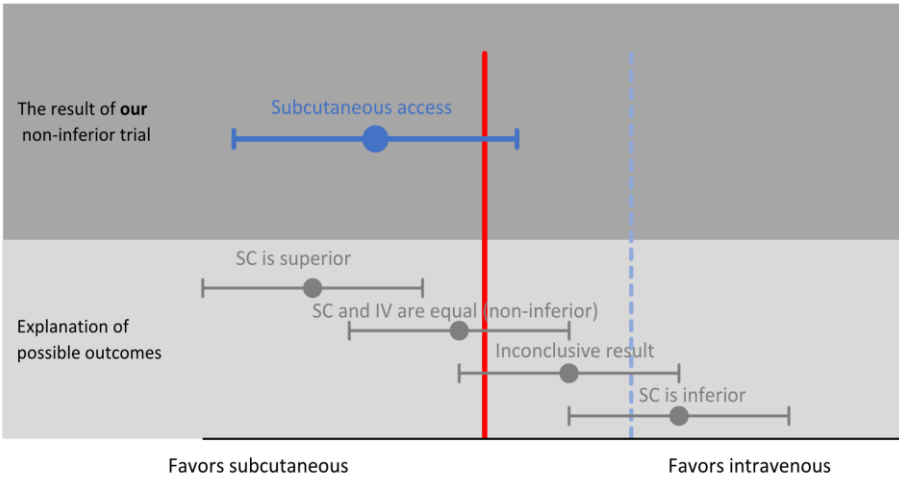
**Table 3. Baseline data of included patients**

| | SC group | IV group |
|---|---|---|
| Age | 79 (7.3) | 83 (6.9) |
| Sex (female)[a] | 16 (66%) | 17 (62%) |
| Number of known comorbidities | 4.6 (1.9) | 3.9 (1.4) |
| Charlson Comorbidity Index[94] Median (25-75 range) | 1 (0-2) | 0 (0-2) |
| Treated with anti-coagulant medication[a] | 8 (35%) | 9 (33%) |
| Systolic Blood Pressure (mm Hg) | 136 (28) | 129 (21) |
| Diastolic blood Pressure (mm Hg) | 68 (10) | 69 (12) |
| Pulse (/min) | 83 (18) | 79 (12) |
| Hemoglobin (mmol/l) | 6.5 (1.4) | 7.0 (1.6) |
| Sodium (mmol/l) | 137 (3.5) | 137 (3.7) |
| Potassium (mmol/l) | 3.8 (0.6) | 3.8 (0.6) |
| Urea (mmol/l) | 8.2 (4.1) | 9.4 (7.7) |
| Creatinine (µmol/l) | 94 (41) | 89 (41) |
| eGFR (ml/min/1.73m$^2$) | 61 (23) | 63 (24) |
| Albumin (g/l) | 25.8 (4.7) | 27.0 (3.6) |
| Osmolality (mmol/kg) | 294 (18) | 290 (11) |

Unless otherwise indicated, data are expressed as mean (standard deviation)

[a]Data expressed as number (percent), table adapted from Study II

**Figure 7.** Graphical presentation of the non-inferiority of subcutaneous vs. intravenous hydration.




Footnote: The solid red line represents the line of no difference between subcutaneous (SC) and intravenous (IV). The dashed blue line represents our pre-specified non-inferiority margin. p-value for non-inferiority = 0.012. The risk ratio between subcutaneous and intravenous is RR 0.66 (95% CI 0.29-1.49) favoring subcutaneous hydration. Figure copied from Study II

**Secondary outcomes**

Our data showed that it is much faster to place the subcutaneous catheter than the intravenous catheter (p=0.001). However, there was no significant difference in the risk of delirium based on CAM scores. The pain reported for insertion of the randomized catheter was not significant either. No patients died during their admission and no patient experienced an incidence of bleeding. See table 4 for all secondary outcomes.

**Table 4.** Secondary outcomes

| **Outcome** | | **Subcutaneous group n(%)** | **Intravenous group n(%)** | **Difference (95% CI)** | **p-value for difference** |
|---|---|---|---|---|---|
| Time spend on insertion[a] | < 5 min:<br>5-20 min:<br>> 20 min[b]: | 18 (85%)<br>2 (10%)<br>1 (5%) | 7 (32%)<br>9 (41%)<br>6 (27%) | N/A | 0.001 |
| Delirium | | 0 (0%) | 3 (14%) | | 0.23 |
| | | **n, mean (SD)** | **n, mean (SD)** | | |
| Pain of insertion (0-100 VAS) | | n=21, 7.3 (10.4) | n=20, 13.0 (13.4) | 5.7 (-1.9; 13.2) | 0.13 |
| Discomfort during infusion (0-100 VAS) | | n=18, 4.5 (11.8) | n=18, 4.7 (7.5) | 0.2 (-6.9; 4.5) | 0.74 |

Abbreviations: VAS: Visual analog score, N/A: Not applicable

[a]Original groups are collapsed due to the low number of events in some groups.

[b]Requiring assistance from another staff member

Table adapted from Study II

## 4.1. SUBCUTANEOUS HYDRATION'S PHYSIOLOGY – STUDY III

**Participants**

We recruited six patients with a mean age of 81 years. Patients were frail with a mean Tilburg frailty scale[59] of 3.8, a mean number of comorbidities of 4.6, and a mean Charlson Comorbidity Index[94] of 1.8. See table 5 for baseline values of included patients. None of our patients experienced any discomfort or adverse effects during the trial. In one participant, the catheter for blood samples coagulated, and further blood samples were not available in this patient.

**Table 5.** Baseline values of the six patients**.**

| | Mean (SD) |
|---|---|
| Number of patients | 6 |
| Age | 81 (2.1) |
| Sex (male/female) | 3/3 |
| Number of known comorbidities | 4.6 (1.2) |
| Charlson Comorbidity Index[94] | 1.8 (1.3) |
| Tilburg frailty scale [95] | 3.8 (2.4) |
| Number of prescription drugs | 10 (4.1) |
| Treated with anti-coagulant medication | 1 (16.7%) |
| Systolic Blood Pressure (mm Hg) | 122 (9.8) |
| Diastolic Blood Pressure (mm Hg) | 71 (5.7) |
| Pulse (/min) | 81 (21) |
| C-reactive protein (mg/l) | 62 (38) |
| Hemoglobin (mmol/l) | 6.2 (0.6) |
| Sodium (mmol/l) | 141 (1.6) |
| Potassium (mmol/l) | 3.9 (0.2) |
| Urea (mmol/l) | 9.3 (2.2) |
| Creatinine (µmol/l) | 97 (42) |
| eGFR (ml/min/1.73m$^2$) | 62 (24) |
| Albumin (g/l) | 28 (4.2) |
| Osmolality (mmol/kg) | 297 (5.5) |

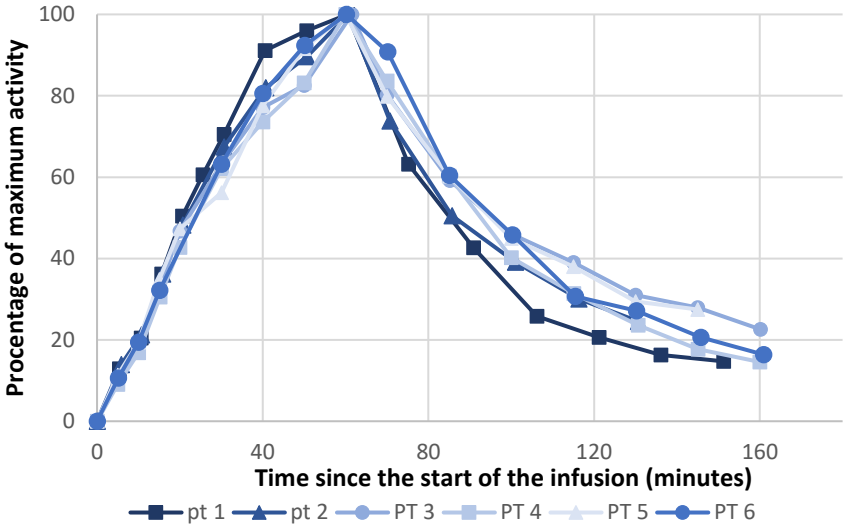
**Absorption rate**

The amount of fluid in the subcutaneous space increased during the infusion and then declined after its completion. At the completion of the infusion, a mean volume of 111 ml was still present in the subcutaneous space. Figure 8 shows the normalized activity at the infusion site over time. We calculated a mean absorption rate right after the end of the infusion of 127 mL/h based on measurement from the infusion site. At the same time point, we calculated a mean absorption rate into the bloodstream of 128 mL/h based on the numbers from blood and 116 mL/h based on data from the thyroid gland. Figure 9 and 10 shows the normalized activity in blood and over the thyroid gland, respectively.

**Regression analyses**

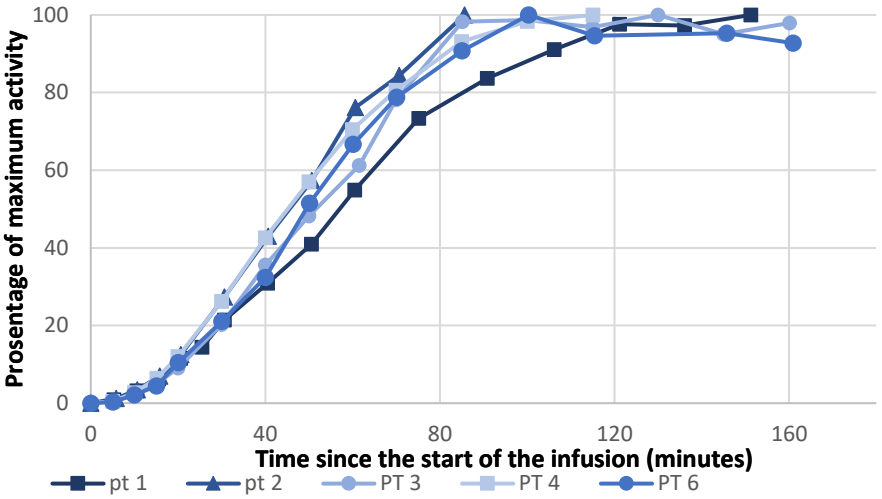
From logistic regression, we found that half of the total amount of infused fluid was available in the blood 48 minutes after the start of infusion based on data from blood and 58 minutes based on data from the thyroid gland. Finally, we found that abound 10% of the infused fluid remained in the subcutaneous space with a prolonged absorption rate. Figure 11 shows the percentage of fluid absorbed over time.

**Figure 8**. Activity at the infusion site over time



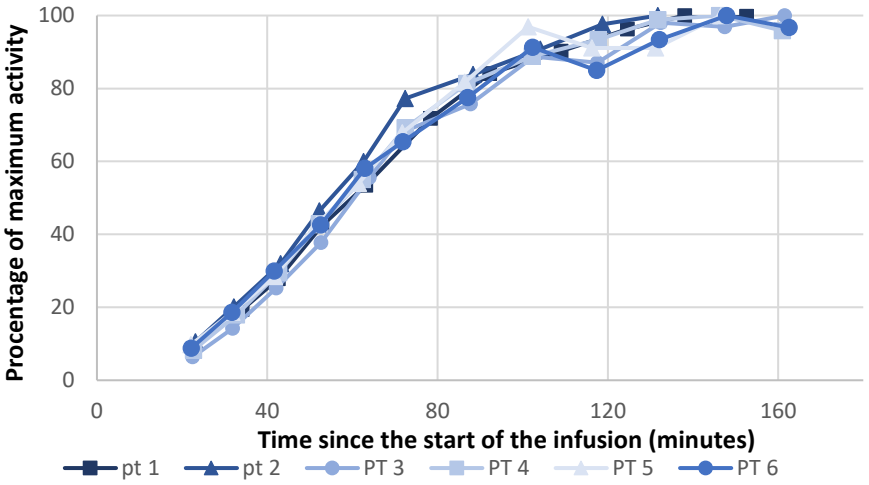

Abbreviation: PT: Patient. Graphical representation of the activity over the infusion site. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity. Copied from study III.

**Figure 9.** Activity in the blood over time



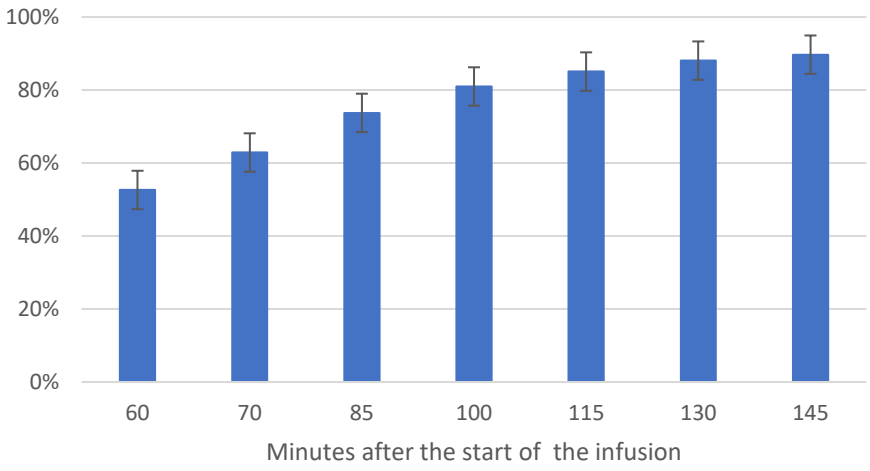

Abbreviation: PT: Patient. Graphical representation of the activity in the blood. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity. Data from patient number 5 is missing as the indwelling catheter for the collection of blood samples clotted. Copied from study III.

**Figure 10.** Activity in the thyroid gland measured over time




Abbreviation: PT: Patient. Graphical representation of the activity over the thyroid gland. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity. Copied from study III.

**Figure 11.** The mean percentage of infused fluid absorbed over time.




Footnote: The X-axis is in minutes after the start of the infusion. The Y-axis is in percent of total infused fluid. I-bars represent standard error. Copied from study III.

## 4.1. UPDATED META-ANALYSES

The inclusion of our RCT in the meta-analyses on adverse effects and the risk of agitation makes no relevant change in the estimate or the confidence interval. The updated risk ratio for adverse effects is 0.68 (95% CI 0.53 to 0.87, $I^2$= 0.0%, figure 12A) when excluding the study with a high risk of bias. The update risk ratio for agitation is 0.41 (95% CI 0.23 to 0.73, $I^2$= 51.5%, figure 12B). The estimate for the reduction of serum osmolality is no longer significant in favor of intravenous hydration. The updated mean difference is 3.49 mmol/kg in favor of intravenous hydration (95% CI -0.72 to 7.7, $I^2$= 0.0%, figure 12C.)

**Figure 12A.** Meta-analysis on the risk of adverse effects including data from our RCT

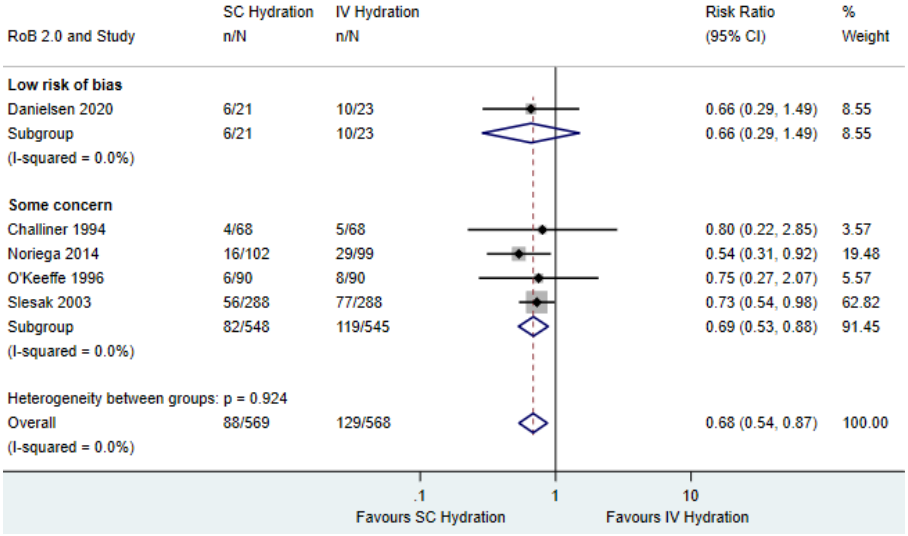



**Figure 12B.** Meta-analysis on the risk of agitation including data from our RCT

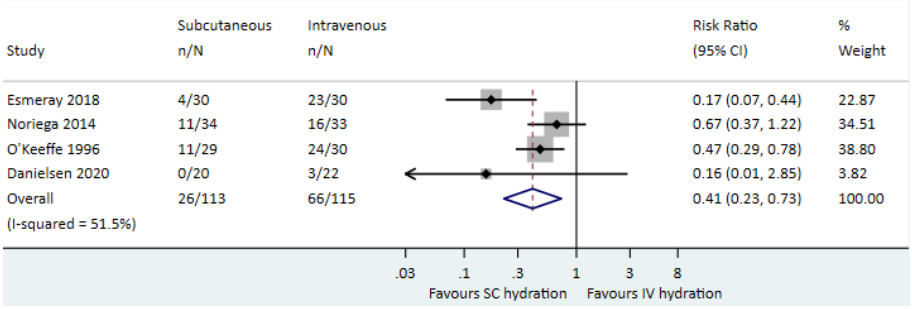
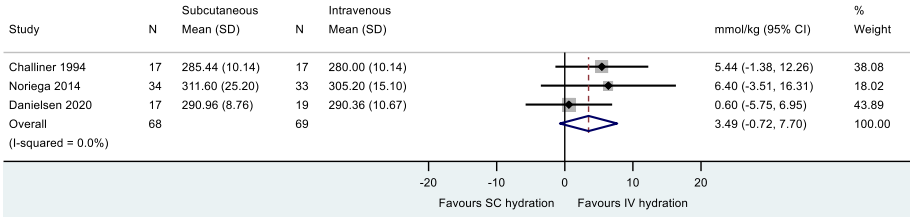



**Figure 12C.** Meta-analysis on the effect on serum osmolality, including data from our RCT




Footnote: Abbreviations: CI: Confidence Interval, N: number of patients, n: number of events, SD: standard deviation.
Meta-analyses of using the random effects inverse-variance model with DerSimonian-Laird estimate of $tau^2$. The dashed line represents the overall pooled estimate.

# CHAPTER 5. DISCUSSION

This chapter begins with a short discussion of the limitations and methodological considerations of this PhD's three individual studies. The conclusion of the individual studies follows this. The subsequent section of the chapter will combine the results of the three studies and discuss the PhD's overall findings. Finally, the future directions for the research on subcutaneous hydration will be considered.

## 5.1. LIMITATIONS AND METHODOLOGICAL CONSIDERATIONS

### 5.1.1. SYSTEMATIC REVIEW – STUDY I

We found two RCTs, six observational studies, and one case report written in languages other than English. Our results would have been different if those were excluded due to language. During the work on this paper, the Cochrane Risk of Bias version 2 was published, and we updated the risk of bias evaluation from version 1 to version 2. This change was done at the request of a reviewer and to ensure the longevity of our review. However, performing the meta-analysis with Risk of Bias version 1 compared to version 2 made no difference in the results. Evaluating the observational studies' risk of bias was more difficult as the risk of bias evaluation tool for this type of study is aimed at observational studies of interventions and not cohort studies. Therefore, there is a relevant risk that a different result can be found in the information from the observational studies since the risk of bias can more easily be evaluated differently by others compared to the risk of bias from RCTs.

**Conclusion of study I**
Subcutaneous hydration is a safe alternative to intravenous hydration but might be less effective. However, we only found a few RCTs on the subject and non with a low risk of bias. Despite this, there was a moderate level of confidence in the estimate on the risk of adverse effects.

### 5.1.2. RANDOMIZED CONTROLLED TRIAL – STUDY II

The trial's primary limitation was the short observation period compared to standard hydration therapy in geriatric patients. Furthermore, many patients were excluded due to an inability to provide informed consent. This reduced our results' external validity, especially on the outcome of delirium, as this condition or cognitive impairment is relatively common in geriatric patients.

The non-inferior trial design is uncommon but a relevant trial design when an intervention has an advantage compared to the alternative, but it is unclear whether the risk is worth the reward. In patients with difficult intravenous access, it is usually relatively easy to place a subcutaneous catheter. We believe subcutaneous hydration has a clear indication for use if it is not harmful to the patient. This made the non-inferior design well suited for our research question. The value of blinding in randomized trials is questioned in a recently published paper that found that blinding provided no benefit.[96] However, blinding is still recommended and required in all tools evaluating the risk of bias to receive a low risk of bias.[51,59,60]

**Conclusion of study II**
Our randomized controlled trial found that subcutaneous hydration is not inferior to intravenous hydration on the outcome of adverse effects. This means that subcutaneous hydration can safely be used as an alternative method for hydration in geriatric patients. Our trial also provides evidence that subcutaneous hydration is significantly faster to place than intravenous hydration, underlining our choice of a non-inferior design.

### 5.1.3. SUBCUTANEOUS HYDRATION'S PHYSIOLOGY – STUDY III

The major limitation of this study is the explorative nature and the low number of participants. However, we found markedly similar results in all patients. Furthermore, we infused a smaller volume of fluid than used in clinical practice. We cannot know if an infusion of an increased volume would change some of the results found in our study.

It would be interesting to compare the infusion into the subcutaneous space with intravenous infusions; however, as our patients are admitted to the hospital and currently ill, their status will change within a short timeframe, hence why the repetition of the infusion as an intravenous infusion a week after would not be comparable. Alternatively, the study could be made as an RCT where patients were randomized to either intravenous or subcutaneous, and then the absorption rates could be measured. However, such a trial would be a large undertaking, and it should be carefully considered if the results would be worth the time and effort invested.

**Conclusion of study III**
Our results show that a relevant absorption rate is found with subcutaneous infusions in frail older adults with comorbidities. This is in line with our clinical experience; however, we found that around 10% of the infused fluid is left in the subcutaneous space with a prolonged absorption rate. Furthermore, measurements from the thyroid gland could be used as an alternative to drawing blood samples in future studies on

the absorption of subcutaneous infused fluid only with a slight time delay in response. This could be relevant as thyroid measurements are non-invasive.

## 5.2. COMBINED DISCUSSION

### 5.2.1. SAFETY OF SUBCUTANEOUS HYDRATION

The PhD's main finding is that subcutaneous hydration is a safe alternative to intravenous hydration in older patients with impending or mild dehydration. The meta-analysis that included data from our RCT found a 32% lower risk of adverse effects with subcutaneous hydration compared to intravenous. Based on the GRADE guidelines, our confidence in this estimate is moderate. Serious adverse effects where patients require additional treatment or prolonged hospitalization are very uncommon, with only a few per thousand infusions. Our RCT's data made no relevant change to the estimate or confidence interval of the risk of adverse effects; however, our results cooperate with previous trials in an RCT adhering to current guidelines, including assessor blinding, preregistering of outcomes, and statistical analysis plan. Whether the inclusion of our RCT changes the GRADE estimation requires an unbiased evaluation. The absolute number of adverse effects is low, with 90 episodes per thousand infusions. This translates to a number needed to harm of 25. This number is dependent on what is counted as an adverse effect and should be interpreted as such. Regardless, the type of adverse effects the number need to harm is based on are primary minor nuisances to the patients. Based on the GRADE evaluation of moderate confidence in the estimate, future studies are likely to influence the estimate. However, I believe that the recommendations that subcutaneous hydration is a safe alternative to intravenous hydration remain unchanged if the true estimate is within the confidence interval. I would argue that there is little need for future studies on the risk of adverse effects comparing intravenous with subcutaneous hydration in the hospitalized older patient.

Two other systematic reviews were published in 2020. One of them only found three RCTs to include but did not combine the various adverse effects into one outcome making their result difficult to compare with ours.[97] The other review was an umbrella review. They concluded that subcutaneous hydration has equal risk of adverse effects as intravenous. They did not perform a meta-analysis and based their result on the result of different original studies.[98] The discrepancy from our results primarily arises from the chosen outcome (combining or not) and our adjusting for the time at risk (by converting the data from the original studies to a risk of adverse effects per infusion). The advantage of combining the adverse effects is that this provides a better understanding of the burden the method may cause the patient. However, if a patient or doctor wishes to avoid a specific adverse effect, the combining removes the ability to choose the most appropriate method. Our decision to convert data to time at risk

may introduce a wrong conversion factor. However, most indwelling catheters will give rise to an adverse effect if left inserted long enough. Not converting data but providing results as adverse effect per patient treated may give an erroneous result as indwelling time is not factored in.

### 5.2.2. PLACEMENT OF CATHETER

Both data from our meta-analysis of the systematic review and data from an RCT show that the subcutaneous catheter is significantly faster to place than an intravenous catheter. When including the data from our trial, the GRADE evaluation of this outcome is likely to change. Based on the data from previous trials and ours (where almost all the subcutaneous catheters were placed in under five minutes and a large portion of intravenous catheters took much longer), it is likely, the advantage of faster catheter insertion with the subcutaneous catheter is primarily based on a portion of the patients where intravenous access is difficult. The main take-home message from these results is not the time saved with subcutaneous hydration but rather the increased number of locations where subcutaneous hydration will be an available method despite not having any personal with the required skill and routine placing intravenous catheters.

The umbrella review reported no difference in inserting time between intravenous and subcutaneous catheters.[98] It is unclear what study they are basing this conclusion on, but they agree with us that the time spent on insertion might not be the relevant factor but rather by who or where parenteral hydration can be used.

### 5.2.3. EFFECT OF SUBCUTANEOUS HYDRATION

Subcutaneous hydration seems less effective than intravenous hydration. This is based on both data from our systematic review where we found a reduced volume of fluid infused, and from our exploratory study on the absorption rate where we found that around 10% of the infused fluid is left in a subcutaneous pocket with a much slower absorption rate than the first 90% of the infused fluid. Our data from the RCT changed the estimate of the reduction of serum osmolality when treating with intravenous vs. subcutaneous hydration. Our data both lowered the increased effects intravenous hydration had and made the result not statistically significant. However, it is unlikely that our result changes the GRADE evaluation of this outcome as the inclusion of our data changes the confidence interval to include the line of no difference. Some of the discrepancies between the trial's results may arise from the difference in the include patients. One of the trials had post-treatment serum osmolality of 310 mmol/kg. These values are usually interpreted as a patient with moderate to severe dehydration; however, we could not gather information on which method the serum osmolality was estimated or measured by in this trial. Both the data from our systematic review and

our exploratory study indicate that subcutaneous hydration is only relevant for patients with impending or mild dehydration. In these patients, the incomplete or prolonged absorption of the last 10% of the infused fluid is without clinical relevance. Finally, evaluating the hydration status of a geriatric patient with a single marker is very difficult, and therefore these results should be interpreted with caution.

Comparing our results with the reviews published in 2020, one of them reported less ability of subcutaneous hydration of lowering serum osmolality[97] while the umbrella review report no difference in biochemical restoration, clinical improvement, and volume of infused fluid. The umbrella review sums up the findings of the individual included studies where most of them are inconclusive without performing any meta-analyses. This difference in the method may explain the slight disagreement with our result.

### 5.2.4. SUBCUTANEOUS HYDRATION AND THE RISK OF DELIRIUM

One of the most exciting and potentially important findings of this PhD thesis is the potential reduction in delirium when treating with subcutaneous vs. intravenous hydration. Most data on this outcome are not new, and our trial provided only minimal additional information on the subject. However, the possibility that subcutaneous hydration can reduce the risk of delirium in geriatric patients by half is a potential game-changer. However, based on the GRADE evaluation, the true effect might be markedly different from the estimated effect. Future studies on the subject should discuss what the least clinically significant difference in this reduction would be. Delirium is a prevalent condition in the geriatric patient, and maybe as little as a 10% reduction by changing the method for hydration could be well worth the time. The umbrella review report that subcutaneous hydration reduced the risk of agitation[98], but neither this review nor those published previously[31,50,99] emphasizes the potential of this result.

## 5.3. FUTURE DIRECTIONS

Some of the unanswered questions in this PhD thesis are what is keeping subcutaneous hydration from being a mainstay in both hospital care of the older patient and when treating patients in the primary sector in long-term care facilities or nursing homes. Based on our experience, there is a lack of knowledge and potentially both a logistical and legal challenge hindering the used subcutaneous hydration. Future studies could investigate which barriers there are to the implementations of subcutaneous hydration.

Based on the results presented in this PhD thesis, it seems unlikely that the risk of adverse effects with subcutaneous hydration versus intravenous hydration will change relevantly with future studies. However, the effect subcutaneous hydration could have

on reducing delirium risk is undoubtedly deserving of further attention. However, this is a complex subject to investigate as it - under Danish laws - requires informed consent from a patient group that is often unable to provide informed consent.

There are still unanswered questions regarding the effect of subcutaneous hydration on the hydration status; however, these questions are difficult to answer without an objectively gold standard for evaluating hydration status in the older patient.

# CHAPTER 6. CONCLUSIONS AND PERSPECTIVES

This PhD thesis provides an updated overview of the available literature on subcutaneous hydration. We believe that subcutaneous hydration has a relevant role in the healthcare system, where shorter admission and increased treatment in the primary sector are gaining attention. Consequently, there is an increased tendency for earlier change from intravenous antibiotics to oral antibiotics where subcutaneous hydration could be relevant co-treatment that follows patients out into the primary sector. This thesis helped fill some of the literature gaps, but further research is needed to estimate subcutaneous hydration's true effect on the risk of delirium.

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# APPENDICES

# Appendix A. Study I



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# Harms and Benefits of Subcutaneous Hydration in Older Patients: Systematic Review and Meta-analysis

## Running title: Subcutaneous Hydration in Older Patients

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## Abstract

**Objective:** To review all available original publications on the harms and benefits of subcutaneous (SC) hydration in older patients**.**

**Design:** Systematic review and meta-analysis.

**Participants:** All studies on SC hydration in older patients without restrictions on design or language.

**Measurements:** The Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science databases, and trial registries were searched from inception to 5 November 2019, and two reviewers independently extracted the data and assessed the risk of bias of individual outcomes.

**Results:** Thirty-one publications from 29 studies met the eligibility criteria. The data from six randomized controlled trials were used for the meta-analyses. The subgroup analysis including only the studies with the lowest risk of bias showed that SC hydration was associated with fewer adverse effects than intravenous (IV) hydration (RR 0.69, 95% CI 0.53-0.88, p=0.003, n=4, $I^2$ =0.0%, 545 infusions in each group). In absolute numbers, patients treated with SC hydration had an incidence rate of 90 adverse effects per 1000 infusions vs. 130 adverse effects per 1000 infusions (95% CI 102-169) with IV hydration. Secondary outcomes comparing IV to SC hydration showed that SC was 3.2 minutes faster to set up, markedly reduced the risk of agitation (RR 0.42, 95% CI 0.22-0.79, p=0.007, $I^2$=65%, n=3); however, delivered a lower volume of fluid, and was less efficient at reducing s-osmolality.

**Conclusions: SC** hydration is safer than IV hydration and potentially reduces the risk of agitation, but it is less effective. SC hydration should be available as an alternative to IV when treating older patients for mild-to-moderate dehydration. More high-quality studies are needed in the field to increase the confidence in the estimates.

**Primary funding source:** Department of Clinical Medicine, Aalborg University and Department of Geriatric Medicine, Aalborg University Hospital. (PROSPERO: CRD42017071912)

Key Words: Hypodermoclysis, Older patients, Hydration treatment, systematic review, meta-analysis

## Introduction

Dehydration is a common and potentially dangerous condition in older patients.[3] A hallmark of aging is a reduced sensation of thirst. The consequences are augmented by the reduced ability of the aging kidneys to concentrate urine.[5] The infusion of fluid is required when oral rehydration is insufficient. Intravenous (IV) hydration is the common choice because large volumes of fluid can be infused, and intravenous medication can be simultaneously administered. However, an alternative choice is subcutaneous (SC) hydration, in which fluid is infused into the subcutaneous space and absorbed into the bloodstream.[55] This often-forgotten method has been reported in recent decades as an easy and safe method for parenteral hydration among geriatric patients with mild-to-moderate dehydration or at risk of dehydration.[31,50,100] Despite these studies, SC hydration is still reported to be underused.[47,48,101]

Fluid infused subcutaneously reaches the circulatory system within an hour, according to the results of a radioisotope study[55]. Hence, the hydration effect should be similar between SC- and IV-infused fluid, but a small delay may occur with SC infusion. There may be clinically relevant differences in the risk of adverse effects between IV and SC hydration. In our experience, it seems that the risk of adverse effects is the main reason for the limited use of SC hydration.

Previous reviews on SC hydration in older patients were published prior to the general acceptance of current guidelines (PRISMA[57], GRADE[59], Cochrane Risk of Bias[60])[50,100] or were narrative reviews without a critical appraisal of included studies.[31] Therefore, we conducted a systematic review and meta-analysis to evaluate the literature based on the newest guidelines. The primary aim of this systematic review was to compare the risk of adverse effects between SC and IV hydration in older patients and to estimate the incidence and profile of adverse effects. The additional aims were to compare the clinical effects of SC and IV hydration. Thus, the overall aim was to assess whether SC hydration is a safe and clinically relevant alternative to IV hydration.

## Methods

We followed the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses when reporting harms (PRISMA-Harms) guidelines[57] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria to rate the quality of evidence and present the results.[59] The study was *a priori* registered in PROSPERO (CRD42017071912).

### Eligibility criteria

To achieve a comprehensive overview in accordance with the recommendations of the Cochrane Handbook[58] on reviews of adverse effects, we included relevant studies that used any design (randomized controlled trials (RCTs), observational studies and case reports) and all types of articles (e.g., conference abstracts, letters to the editor). We attempted to contact authors for additional information or full-text publications in cases of short reports, such as conference abstracts. No restriction on language, publication date or settings was imposed, but inclusion was restricted to studies on older patients (age >65 years or mean age >60 years). Furthermore, studies had to include SC hydration as an intervention with hydration as an indication for infusion. We included studies with IV hydration as a comparator or observational studies with no comparator. Studies on the SC infusion of drugs, parenteral nutrition, the relevance of hyaluronidase, or studies without patient information were excluded. Cross-sectional studies and case reports without any information on adverse effects were excluded, as the reason for including these studies was to estimate the incidence and profile of adverse effects.

### Information sources and search

The search strategy was developed in collaboration with a health sciences librarian. We systematically searched the following databases: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. In addition, we searched ClinicalTrials.gov and www.who.int/ictrp for unpublished studies and ongoing trials. Furthermore, we cross-referenced both included studies and relevant reviews for eligible studies. All databases were searched from inception to 5 November 2019. Authors of unpublished and ongoing trials were asked if data were available to be included in this review. The full search strings included the following: Hypodermoclysis, Subcutaneous, Rehydration, Fluid Therapy, Fluid Administration, Infusions, Solutions, Dehydration, Hypovolemia, and Fluid Resuscitation.

### Study selection

Two reviewers (MBD and SA) independently assessed the eligibility of articles by screening the titles and abstracts and then by reviewing the full-texts of relevant articles. Disagreements were settled by consensus or by involving a coauthor (MGJ).

## Data items and collection process

We first translated all non-English publications using a translation engine[102,103], and when the translation was insufficient, a translator provided a written translation. Two reviewers (MDB and SA) independently extracted the data using piloted forms. Data were included only once, even if the data were included in more than one publication. The following data were extracted: study and patient characteristics, type of fluid infused, use of hyaluronidase and duration of treatment. In all studies with missing data, we attempted to contact the authors by e-mail to obtain the relevant information. To estimate exposure, we extracted the total number of infusions. If this information was not reported, we calculated it by multiplying the number of participants by the mean number of days of infusion.

An adverse effect, in general, is defined as "an unfavorable outcome that occurs during or after the use of a drug or other intervention and for which the causal relation between the intervention and the event is at least a reasonable possibility".[58] Additionally, we divided adverse effects into serious and minor effects and adhered to the WHO's definition of serious adverse effects as any consequence of infusion requiring treatment.[104] All outcome data were extracted as intention to treat.

## Risk of bias in individual studies

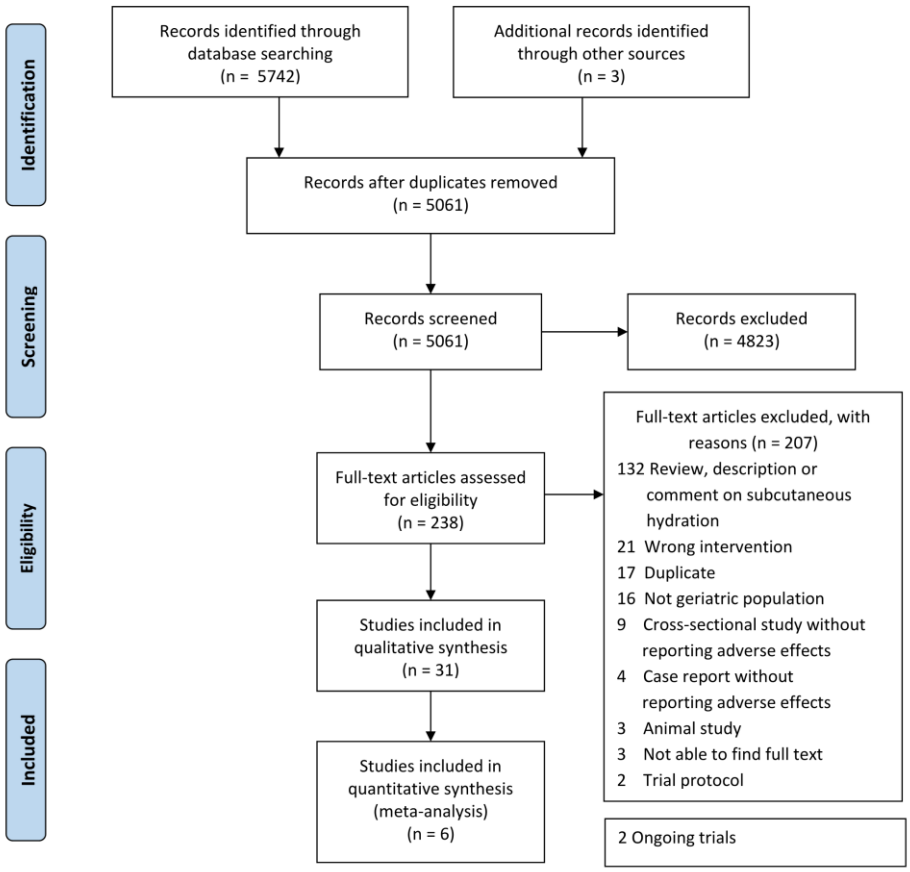
We used the Cochrane Risk of Bias 2.0 (RoB 2) to assess the risk of bias in RCTs[60]; furthermore, we assessed the risk of bias in observational studies based on the key criteria listed by the GRADE[61]. Two reviewers (MD & SA) independently assessed the risk of bias at the outcome level.

## Data synthesis and analysis

To assess whether the RCTs were sufficiently homogeneous and could be combined in a meta-analysis, we compared the studies with respect to the participants, interventions and outcome measures. Only RCTs were included in the meta-analyses. For the meta-analysis, we applied an inverse variance random-effects model (DerSimonian-Laird[105]). Statistical heterogeneity was explored using the $I^2$ statistic. We report dichotomous outcomes as risk ratios (RRs) and continuous outcomes as mean differences (MDs). When the same outcome was reported using different scales, we report the standardized mean difference (SMD). Stata version 15 (StataCorp LLC TX College Station. 2017) and ADMETAN[106] were used to perform the analyses. Comparisons were 2-tailed with statistical significance indicated at 5% and with 95% confidence intervals. The data analysis only included studies reporting both the

number of adverse effects and the number of infusions. As hydration treatment can last several days, a single patient can experience multiple adverse effects. Thus, we analyzed the outcome of adverse effects considering the number of infusions.
As recommended by the Cochrane RoB 2, meta-analyses were stratified by the overall risk of bias.[60] Prespecified subgroup analyses of the primary outcome with regard to the addition of hyaluronidase and the setting of the studies were also conducted. Furthermore, we performed a separate meta-analysis for serious adverse effects as an explanatory analysis.

**Figure 1. PRISMA flowchart**



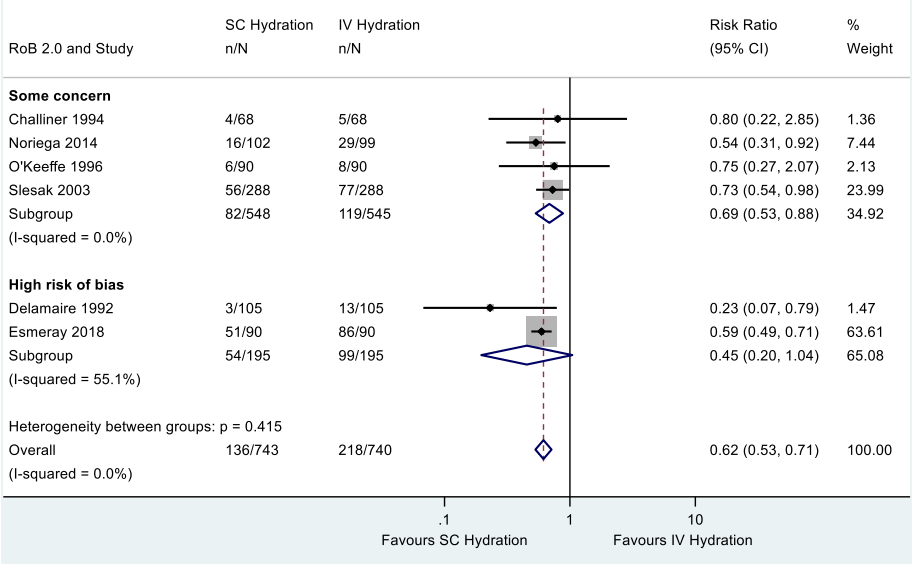

To estimate the incidence of adverse effects associated with SC hydration, we combined data from all included studies by adding the number of reported adverse effects and the number of infusions from all studies. In addition, we estimated the

incidence among only the studies with the lowest risk of bias. We used this incidence and the RR from our lowest risk of bias subgroup meta-analysis to calculate the absolute risk difference according to the GRADE guidelines[107].

## Additional analyses

As dehydration cannot be defined by a single symptom, sign or laboratory value[5,10], we conducted meta-analyses of all available surrogate markers of dehydration and the clinical effect of hydration treatment if the marker was examined in at least two RCTs. Furthermore, we examined the time spent on catheter insertion.

**Figure 2.** Meta-analysis of the number of adverse effects comparing subcutaneous hydration vs intravenous hydration stratified by overall risk of bias.




Footnote: Abbreviations: RoB 2.0: Cochrane Risk of Bias 2.0, n/N: Number of adverse effects/Number of infusions, CI: Confidence Interval, SC: Subcutaneous, IV: Intravenous.
Meta-analysis of pooled risk ratios using the random effects inverse-variance model with DerSimonian-Laird estimate of $tau^2$.
The dashed line represents the overall pooled estimate.

## Results

### Study selection

A total of 5061 references were retrieved from the search. After the titles and abstracts were screened, 238 articles were selected for full-text screening (figure 1. PRISMA flow chart[108]). Most publications excluded during full-text screening were reviews or descriptions of subcutaneous hydration. In addition, there were nine cross-sectional studies and four case reports with no information on adverse effects. Furthermore, we found two relevant study protocols: one study had no data yet[109], and the author of the other study e-mailed us a poster but had no full-text report. The poster had insufficient data to be included in the meta-analysis[110]. We thus ended up with thirty-one publications representing 29 different studies.

### Study characteristics

The designs of the 29 included studies were as follows: 7 RCTs[41,42,46,70–73], 1 case-control study[45], 11 prospective cross-sectional studies[44,74–83], 6 retrospective cross-sectional studies[40,43,84–89] and 4 case reports[90–93]. Fourteen studies were performed in a hospital setting, six studies were performed in short-/long-term care facilities, eight studies included a combination of hospital and short-/long-term care or home-based treatment, and one study did not report the setting. The median age of patients in the included studies was 82 years (range 61-85). The median number of patients included was 57 (range 8-634), and the median number of SC infusions was 252 (range 17-4500), excluding case reports. The use of infusion pumps was not described. Nine studies reported sources of funding, and none were industry sponsored. Of the 23 authors contacted for additional information, 7 responded, and most provided only a partial response.

One RCT, four prospective studies and one retrospective cross-sectional study either did not report enough data for use to estimate the number of infusions or did not report the number of adverse effects. None of these authors responded to our requests for additional information. Hence, these studies were not included in the data synthesis. Table 1 provides a summary of the characteristics of the included RCTs.

**Table 1** Characteristics of the included RCT studies

| **Study & year** Country Language | **Sample size** (number of infusions) | **Setting** | **Patient population characteristics** | **Intervention (I) and comparator (C) details** | **Duration of intervention/ comparator** |
|---|---|---|---|---|---|
| **Delamaire 1992**[70] France French | **30** (105 infusions in each group[a]) | No description of setting | Geriatric patients. Described as elderly patients. No information on participants' hydration status. Mean age: 83 years No information on sex | **I:** SC infusion (no further description). **O:** IV infusion (no further description). | Mean: 7 days, SD: No data |
| **Challiner 1994**[41] United Kingdom English | **34** (68 infusions in each group[b]) | Hospital, elderly care unit | Geriatric patients with acute stroke. Dehydrated (mean s-osmolality 296 mmol/kg at baseline) Mean age 83.5 years Male: 23, Female: 11 | **I:** SC infusion. Two liters of fluid per 24 hours delivered through a 19 G butterfly. **O:** IV infusion. Two liters of fluid per 24 hours delivered through an IV access (no further information). | 48 hours (predetermined) |
| **O'Keeffe 1996**[42] United Kingdom English | **60** (90 infusions in each group[c]) | Hospital, acute geriatric unit | Geriatric patients with cognitive impairment. Mild dehydration or poor oral intake (mean s-urea 28 mg/dl, mean s-creatinine 1.2 mg/dl at baseline) Mean age 82.5 years Male: 23, Female: 37 | **I:** SC infusion. Up to 2 liters of fluid per 24 hours. 21 G butterfly needle in infraclavicular, scapular, abdominal or thigh areas. **O:** IV infusion. Up to two liters of fluid per 24 hours. 18-20 G cannula in forearm veins. | 48 hours (predetermined) |
| **Slesak 2003**[46] Germany English | **96** (288 infusions in each group[a]) | Hospital, geriatric wards in the Geriatric Department | Geriatric patients with signs of mild-to-moderate dehydration (median s-creatinine 1.0 mg/dl at baseline) Mean age 85.3 years Male: 29, Female: 67 | **I:** SC infusion. Up to 1.5 liters of fluid per 24 hours. Butterfly needle 21 G, in SC tissue of thigh, abdomen, or thorax. **O:** IV infusion. Up to 1.5 liters of fluid per 24 hours. Peripheral IV catheters 18-22 G. | Median 6 days, range 1-36 days |
| **Luk 2008**[72] China English | **57** (number of infusions unable to be calculated) | Hospital | Geriatric patients with mild-to-moderate dehydration. (mean urea/creatinine ratio 0.11 (IV group) 0.14 (SC group) at baseline) Mean age: 85 years Male: 34, Female: 23 | **I:** SC infusion. Up to 1.5 liters of fluid per 24 hours. 22 G butterfly needle in the SC tissue of the lateral abdomen. **O:** IV infusion. Up to 1.5 liters of fluid per 24 hours. 18-22 G angiocaths. | Up to 3 days (Predetermined) |
| **Noriega 2014**[73] Spain Spanish | **70** (102 infusions in SC group, 99 infusions in IV group[a]) | Hospital, acute geriatrics unit | Geriatric patients, dehydrated (mean s-osmolality 327 mmol/kg, mean s-urea 108 mg/dl, mean s-creatinine 1.9 mg/dl at baseline) Mean age: 85.4 years Male: 35, Female: 32 | **I:** SC infusion. Up to 1.5 liters of fluid per 24 hours. Butterfly needle 21-25 G, in SC tissue of thigh, abdomen or scapular. **O:** IV infusion. Up to 1.5 liters of fluid per 24 hours. Peripheral IV catheters 20-24 G in forearm or hand. | 3 days, (Predetermined) |
| **Esmeray 2018**[71] Turkey English | **30** Crossover RCT (90 infusions in each group.) | Long-term care "Private long-stay geriatric care unit" | Geriatric patients with dementia. 60% were dependent on support for fluid intake. Mild/moderate dehydration or risk of dehydration. No further information on participants' hydration status. Mean age: 82 years Male: 3, Female: 27 | **I:** SC infusion. 21–23 G butterfly needle **O:** IV infusion. (No further information). | Three SC infusions and three IV infusions. No data on how long this took. |

Abbreviations: RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, G: Gauge. A short description of the outcomes available for extraction can be found in Supplementary Table S1.

[a] Calculated based on the number of participants per group x mean duration of intervention.

[b] Calculated based on the number of participants per group x two infusions per day x two days of infusions.

[c] Number of infusions calculated by the number of participants x 1.5 per day per group.

## Risk of bias within studies

For the outcome of adverse effects, four of six RCTs had of *Some Concern of bias*[41,42,46,73] and two had a *High risk of bias*[70,71] according to the RoB 2. Across all outcomes, no studies reported an *a priori* protocol or statistical analysis plan. In addition, descriptions and measurements of outcomes were generally lacking. Thus, all studies had shortcomings compared to current recommendations.

## Synthesis of results

### Adverse effects

When the data from the six RCTs[41,42,46,70,71,73] were combined in a meta-analysis, the studies with the lowest overall risk of bias (*Some concern, n=4*) showed a 31% lower risk of adverse effects with SC hydration than with IV hydration (RR 0.69, 95% CI 0.53 to 0.88, test for effect p=0.003, $I^2$=0.0% n=4, Figure 2 and Table 2). The RCT not included in the meta-analysis as it did not report the number of adverse effects observed, reported that there was no difference in observed complications between the hydration methods.[72]

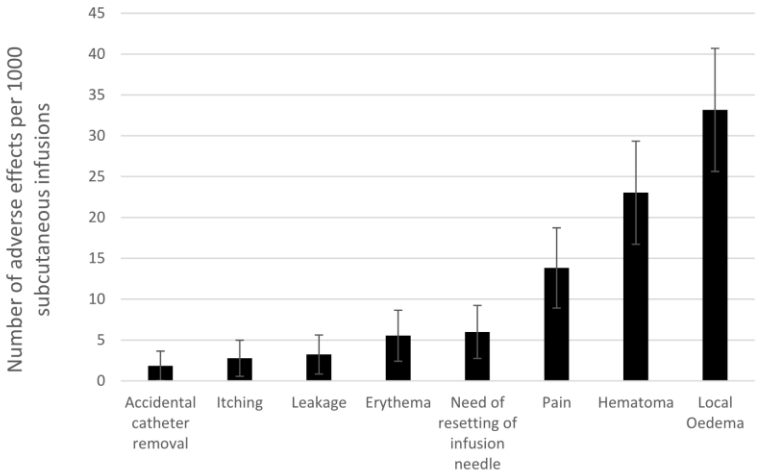
By combining all the six RCTs and the thirteen observational studies with suitable data[40–43,45,46,70,71,73,75–78,80,82,83,85–89] the incidence rate for SC hydration in absolute numbers was 53 adverse effects per 1000 infusions (95% CI 48 to 57, n=19, 10,970 infusions). The incidence rate among only the studies with the lowest risk of bias (four RCTs and four observational studies)[41,42,45,46,73,76,80,82] was 90 adverse effects per 1000 SC infusions (95% CI 80 to 101, n=8, 2876 infusions). In comparison, patients treated with IV hydration experienced 130 adverse effects per 1000 infusions (95% CI 102 to 169, table 2). Details on the incidences of minor adverse effects in studies with the lowest risk of bias are shown in Figure 3.

Among all included studies with suitable data, the incidence rate of serious adverse effects among patients treated with SC hydration was 2.2 adverse effects per 1000 SC infusions (95% CI 1.3 to 3.1, n=20, 10,970 infusions); among only the studies with the lowest risk of bias, the incidence rate of serious adverse effects among patients treated with SC hydration was 3.7 adverse effects per 1000 SC infusions (95% CI 1.5 to 5.9, n=8, 2876 infusions). Furthermore, a meta-analysis suggest that patients treated with SC hydration have a lower risk of serious adverse effects than those treated with IV hydration (risk ratio 0.5, 95% CI 0.2 to 1.2, p=0.13, n=3, 743 SC and 740 IV infusions).

It is noteworthy that the included case reports described 1 case of cecal perforation due to SC hydration in a lean 86-year-old female[90] and 1 case of erythema progressing to necrosis due to SC hydration[91].

In summary, the data indicate that adverse effects are markedly less frequent in patients treated with SC hydration than in those treated with IV hydration.

**Figure 3.** Incidence of minor adverse effects per 1000 infusions




Footnote: Data from the studies with the lowest risk of bias (in total n = 7, with 2171 infusions)[41,42,46,73,76,80,82]. I-bars represent the 95% confidence interval. One study reported data on serious adverse effects and the total number of minor adverse effects but not on specific minor adverse effects[45]. This caused the discrepancy between the number of included studies and infusions in figure 3 and the reported incidence of 90 per 1000 infusions.

**Clinical effects of the hydration treatment**

The included studies used an array of surrogate markers of dehydration in an attempt to evaluate how well SC and IV hydration treated the problem. However, most of these markers were reported in a nonuniform manner, making them unfit to include in a meta-analysis. S-osmolality was reported sufficiently to be combined in a meta-analysis; the findings indicated that IV hydration led to a significantly greater decrease in s-osmolality than SC hydration (MD 5.75 mmol/kg, 95% CI 0.13: 11.37, p=0.045, Table 2)[41,73]. The other surrogate markers of dehydration examined were creatinine levels[42,46,73], urea levels[42,73], patient discomfort[46] and the Barthel Score[46];

no statistically significant differences were reported between the two hydration methods for any of these variables.

Table 2 presents data that illustrate that death rates did not differ between SC and IV hydration (RR 1.26, 95% CI 0.25: 6.34, p=0.78)[41,42,73]. The volume of fluid infused[42,46,73] was higher among patients treated with IV hydration (SMD 0.62 95% CI 0.24: 1.01, p=0.002)[42,46,73]. Agitation among patients with cognitive impairment was lower after SC hydration (RR 0.42, 95% CI 0.22: 0.79, p=0.007)[42,71,73]. Finally, inserting SC catheters took 3.2 fewer minutes than inserting IV catheters (MD 3.2 minutes, 95% CI 1.5: 4.9, p<0.001)[46,71].

In summary, compared to IV, SC hydration appears to be faster to set up; was associated with a lower risk of agitation; however, had a weaker effect on the lowering of s-osmolality; infused less fluid; and showed no association with mortality.

**Risk of bias across studies**

When evaluating the risk of publication bias, we identified one unpublished RCT comparing IV hydration with SC hydration. A poster from this study described fewer complications with SC hydration than with IV hydration. Furthermore, a funnel plot showed no suspicion of publication bias although it is only based on six RCTs.

We found no overall risk of selective reporting bias for adverse effects, as we found no RCT on SC hydration vs IV hydration that did not examine this outcome. However, there was a potential risk that the definitions of outcomes were altered following data collection, as none of the included studies had an a priori registration.

Thus, we found no indication of publication bias or selective reporting bias, but we did find a risk of altering definitions of adverse effects and hydration status.

**Table 2. GRADE Summary of findings: subcutaneous hydration**

| No of studies (design) | n/N of infusions SC | IV | Relative effect measure (95% CI) | Absolute effect | Quality of the evidence |
|---|---|---|---|---|---|
| **Risk of adverse effects** | | | | | |
| Subgroup with lowest risk of bias (4 RCTs) | 82/548 | 119/545 | RR 0.69 (0.53: 0.88) | The incidence of adverse effects with SC is **90** per 1000 infusions compared to **130** per 1000 infusions with IV (95% CI 102-169).[a] | ⊕⊕⊕O Moderate[b,c] |
| | n/N (SC) | n/N (IV) | | | |
| **Effect of treating the problem (dehydration), inferred from the surrogate outcome "Effect on s-osmolality"** | | | | | |
| (2 RCTs) | 51[f] | 50[f] | MD 5.75 (0.13: 11.37) | IV hydration lowers s-osmolality by **5.75** mmol/kg (95% CI 0.13-11.4) more than with SC hydration. | ⊕OOO Very low[b,c,d] |
| **Effect of hydration treatment, "Death"** | | | | | |
| (3 RCTs) | 3/84 | 2/82 | RR 1.26 (0.25: 6.34) | Meaningful absolute values unable to be calculated due to a very large confidence interval. | ⊕OOO Very low[c,d,e] |
| **Effect of the hydration treatment, inferred from the surrogate outcome "Volume of fluid infused"** | | | | | |
| (3 RCTs) | 110[f] | 111[f] | SMD: 0.62 (0.24: 1.01)[g] | IV hydration infuses **155** ml more fluid per day (95% CI 60 ml-253 ml) than SC hydration when infusing 1000 ml/day.[h] | ⊕OOO Very low[b,d] |
| **Effect of the hydration treatment, inferred from the surrogate outcome "Agitation"** | | | | | |
| (3 RCTs)[i] | 26/93 | 63/93 | RR 0.42 (0.22: 0.79) | **68%** patients treated with IV hydration with cognitive impairment experience agitation vs **28%** treated with SC hydration (95% CI 15%-54%). | ⊕⊕OO Low[b,d] |
| **Time spent on catheter insertion** | | | | | |
| (2 RCTs) | 138[f] | 138[f] | MD 3.2 (1.5: 4.9) | Setting up SC hydration takes **3.2** fewer minutes (1.5-4.9) than setting up IV hydration. | ⊕OOO Very low[b,e] |

Abbreviations: RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, CI: Confidence interval, RR: risk ratio, MD: Mean difference, SMD: Standardized Mean Difference.

[a] Based on incidence of adverse effects from SC hydration from the studies with the lowest risk of bias (4 RCTs and 4 observational studies.)

[b] Downgraded due to risk of bias of included studies

[c] Downgraded due to imprecision

[d] Downgraded due to indirectness

[e] Downgraded due to inconsistency

[f] Number of patients evaluated for this outcome

[g] We have use standard mean difference (SMD) as included studies reported either volume per day or volume overall.

[h] Based on numbers from Slesak 2003[46] with 1000 ml ± 250 being infused per day in IV group.

[i] All studies included mostly patients with cognitive impairment.

GRADE Evidence profile table can be found in Supplementary Table S3

## Discussion

### Summary of evidence

Hydration treatment is a cornerstone in the care of older patients, but gaining IV access can be time-consuming in multimorbid patients.[111] SC hydration is a safer alternative than IV hydration, and in absolute numbers SC hydration compared to IV hydration results in 40 (95% CI 12-79) fewer adverse effects per 1000 infusions. We consider this reduction of 31% clinically relevant, and despite many of these adverse effects being minor, such as mild discomfort to the patient or requiring the reinsertion of the needle, it is appropriate to relieve patient discomfort when possible. Based on the GRADE system, the confidence in this estimate is moderate, making it a good estimate of the true effect (Table 2). With both relevant effect size and moderate quality of evidence, clinicians should consider choosing SC hydration over IV hydration in patients with mild to moderate dehydration or at risk of dehydration. Our results support the conclusions seen in previous reviews[31,50,100], and the present meta-analysis and updated evaluation strengthen the recommendations.

A similar incidence of adverse effects was found in the observational studies performed outside the hospital, indicating that SC hydration is a safe option in short- and long-term care settings. The incidence of minor adverse effects displayed in figure 3 is based on data from both RCTs and observational studies and can help guide staff in both hospitals and care facilities on which adverse effects should be assessed.

Serious adverse effects that increased the duration of the hospital stay or required additional treatment were reported in just 1 out of every 270 infusions for both IV and SC hydration. Care should be taken when the SC needle is inserted into the abdomen of cachectic patients, as case reports have described perforation of large intestines when treating very thin patients. Furthermore, the main component that helps to absorb fluid from the subcutaneous space into the blood is albumin.[112] Theoretically, patients with a low level of albumin could have difficulties absorbing SC hydration, and caution is advised despite the lack of evidence.

The main drawback of SC hydration is the restriction of the volume of fluid that can be infused. Guidelines advise a maximum of 1.5 L of fluid per needle per day[5,31], and the listed indication for SC hydration is the treatment of mild-to-moderate dehydration or fluid supplementation in patients with reduced oral intake at risk of dehydration.[5] These indications are supported by our finding that a lower volume of fluid is infused with SC hydration than with IV hydration and by the weaker effect of SC hydration on lowering s-osmolarity. However, the quality of evidence in the comparison of the

effect of hydration treatment between the two methods is very low, making it very likely that the true effect are substantially different (Table 2). Further research is needed to specify the range of the patient group for which SC hydration is relevant.

Interestingly, the 58% lower risk of agitation in patients with cognitive impairment with SC hydration is very promising, as this condition is associated with increased morbidity and mortality.[113] However, the confidence in this estimate is low, and the outcome was reported as agitation and not delirium This outcome is promising and further research on this topic is warranted, as a reduction in the incidence of delirium could have a large impact on both patient outcomes and health resources.

The average time spent on IV catheter insertion was 5.2 minutes; this time was 3.2 minutes less for the insertion of SC catheter. This difference is likely to be relevant given the limited staff resources in modern healthcare. Nevertheless, this result should be interpreted with caution, as the confidence in this estimate is very low (Table 2).

The strengths of the current review are as follows: (1) we performed a comprehensive search; (2) we included all study designs and all article types; (3) we included publications from all languages; (4) we had high methodological standards; and (5) all outcomes were reported in absolute numbers to support clinical interpretation.

## Limitations

### Review level

The description of the statistical method used for the analysis of secondary outcomes in the preregistered protocols was insufficient, and these results should be interpreted with caution.

### Outcome level

A major limitation was the low number of RCTs, but the evaluations were supported by the findings from observational studies. This emphasizes the need for further high-quality studies. Furthermore, most of our analyses were conducted with data from studies with at least *Some Concern* of bias. The incidence of adverse effects could likely have been higher if all studies had reported the full list of events. Finally, we were only able to retrieve additional data from a few of the studies lacking data.

## Conclusion

SC hydration is a safer method for parenteral hydration than IV hydration. The reduced risk of agitation found in patients with cognitive impairment treated with SC hydration compared to that in patients treated with IV hydration is intriguing and supports the use of SC hydration. Nevertheless, more high-quality studies are needed to establish the true benefits and harms of SC hydration.

## Acknowledgments

The authors would like to thank the authors of the included studies who responded to the requests for additional information.

**Conflict of Interest Disclosure:** No authors have any conflicts of interest.

**Authors' Contributions:** *Concept and design:* Danielsen, Andersen, Jorgensen

*Acquisition, analysis, or interpretation of data:* Danielsen, Andersen, Worthington, Jorgensen

*Drafting of the manuscript:* Danielsen, Andersen, Jorgensen

*Critical revision of the manuscript for important intellectual content:* Danielsen, Andersen, Worthington, Jorgensen

**Funding/Support:** This review was funded by the Department of Clinical Medicine, Aalborg University and Department of Geriatric Medicine, Aalborg University Hospital.

**Role of the Funder/Sponsor:** None

**Additional Contributions:** We thank Laura Marie Aalkjær Danielsen for help with translations from French; MLISc Pernille Skou Gaardsted, Medical Library, Aalborg University Hospital for help with developing the search strategy; and Msc Niels Henrik Bruun, Unit of Clinical Biostatistics, Aalborg University Hospital for statistical assistance. All persons who contributed significantly to this work have been mentioned.

**Reproducible Research Statement:** Study protocol available at PROSPERO: CRD42017071912. Statistical code and data set: Available from M. Danielsen MD, Department of Geriatric Medicine, Aalborg University Hospital, Denmark Email: Maad@rn.dk

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## Supporting information

Additional Supporting Information may be found in the online version of this article.

## Brief Legends for supplementary information

- Supplementary Text S1. Search string for the included database
- Supplementary Table S1. Descriptions of outcomes of included RCTs with individual overall risk of bias
- Supplementary Table S2. Risk of bias of cross-sectional studies for the outcome of adverse effects
- Supplementary Figure S1-3. Subgroup meta-analysis by setting of study, use of hyaluronidase and serious adverse effects comparing subcutaneous vs intravenous hydration
- Supplementary Figure S4. Meta-analysis of all the different types of adverse effects comparing subcutaneous vs intravenous hydration
- Supplementary Figure S5-9. Meta-analysis on secondary outcomes (reduction of s-osmolality, death, volume of fluid infused, agitation and time spent of catheter insertion) comparing subcutaneous vs intravenous hydration
- Supplementary Figure S10. Funnel plot for adverse effects from 6 RCTs of subcutaneous vs intravenous hydration
- Supplementary Table S3. GRADE Evidence profile: subcutaneous hydration

**Details on each of the following will be made available upon request to the corresponding author:** Reasons for the exclusion of papers after full-text review; Extracted study characteristics; Judgment of the individual domains in Risk of Bias 2.0 and answers to signaling question

**Supplementary of**

# Harms and Benefits of Subcutaneous Hydration in Older Patients: Systematic Review and Meta-analysis

TABLE OF CONTENTS

# Supplementary Text S1. Search string for included databases.

## MEDLINE search – PubMed interface

("Hypodermoclysis"[Mesh] OR hypodermoclys*[tw]) OR
((”Solutions, Rehydration”[MeSH] OR fluid therap*[tw] OR "Fluid Therapy"[Mesh] OR
"Dehydration"[Mesh] OR dehydrat*[tw] OR
hypovolaemi*[tw] OR hypovolemi*[tw] OR "Hypovolemia"[Mesh] OR
rehydrat*[tw] OR
Fluid Administrat*[tw]) AND
(subcutaneou*[tw] OR “Infusions, Subcutaneous”[MeSH]))

## Cochrane library

| ID | Search |
|---|---|
| #1 | MeSH descriptor: [Hypodermoclysis] explode all trees |
| #2 | hypodermoclys*:ti,ab,kw (Word variations have been searched) |
| #3 | #1 or #2 |
| #4 | MeSH descriptor: [Rehydration Solutions] explode all trees |
| #5 | MeSH descriptor: [Fluid Therapy] explode all trees |
| #6 | MeSH descriptor: [Dehydration] explode all trees |
| #7 | MeSH descriptor: [Hypovolemia] explode all trees |
| #8 | "fluid therap*":ti,ab,kw (Word variations have been searched) |
| #9 | dehydrat*:ti,ab,kw (Word variations have been searched) |
| #10 | hypovolaemi*:ti,ab,kw (Word variations have been searched) |
| #11 | hypovolemi*:ti,ab,kw (Word variations have been searched) |
| #12 | rehydrat*:ti,ab,kw (Word variations have been searched) |
| #13 | "Fluid Administrat*":ti,ab,kw (Word variations have been searched) |
| #14 | #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 |
| #15 | MeSH descriptor: [Infusions, Subcutaneous] explode all trees |
| #16 | subcutaneou*:ti,ab,kw (Word variations have been searched) |
| #17 | #15 or #16 |
| #18 | #14 and #17 |
| #19 | #18 or #3 |

## Web of Science

#1 TS=hypodermoclys*
#2 TS=("fluid therap*" OR dehydrat* OR hypovolaemi* OR hypovolemi* rehydrat* OR "Fluid Administrat*")
#3 TS=subcutaneou*
#4 #3 AND #2
#5 #4 OR #1

## CINAHL

S1 (MH "Hypodermoclysis")
S2 hypodermoclys*
S3 S1 OR S2
S4 (MH "Infusions, Subcutaneous+")
S5 subcutaneou*
S6 S4 OR S5
S7 fluid therap*
S8 dehydrat*
S9 hypovolaemi*
S10 hypovolemi*
S11 rehydrat*
S12 Fluid Administrat*
S13 (MH "Rehydration Solutions")
S14 (MH "Fluid Therapy+")
S15 (MH "Dehydration") OR (MH "Hyponatremia")
S16 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17 S6 AND S16
S18 S3 OR S17

## EMBASE

1. hypodermoclysis/
2. hypodermoclys*.mp.
3. 1 or 2
4. subcutaneous drug administration/
5. subcutaneou*.mp.
6. 4 or 5
7. fluid therapy/ or fluid resuscitation/ or exp parenteral nutrition/ or exp rehydration/
8. dehydration/
9. hypovolemia/
10. fluid therap*.mp.
11. dehydrat*.mp.
12. hypovolaemi*.mp.
13. rehydrat*.mp.
14. Fluid Administrat*.mp.
15. or/7-14

16. 6 and 15
17. 3 or 16
18. remove duplicates from 17

**Supplementary Table S1. Outcomes of included RCT with information on method of measuring, ascertainment and individual Overall Risk of Bias**

| | Adverse effects | | | Death | | | Catheter insertion time | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study & year** Country | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 |
| **Delamaire 1992** France | No description of which adverse effects were observed | No information | – | No description | No information | ! | | | |
| **Challiner 1994** United Kingdom | No description of which adverse effects were observed. | No information | ! | No description | No information | + | | | |
| **O'Keeffe 1996** United Kingdom | No description of which adverse effects were observed. | Assessed by nursing staff. | ! | No description | No information | + | | | |
| **Slesak 2003** Germany | Clear description of which adverse effects were observed. | Assessed by nursing staff and doctors. | ! | No description | No information | + | Measured in minutes. No further description. | No information | ! |
| **Luk 2008** China | Clear description of which adverse effects were observed. | No information | – | | | | | | |
| **Noriega 2014** Spain | Insufficient description of which adverse effects were observed. | Study assessor. | ! | No description | No information | ! | | | |
| **Esmeray 2018** Turkey | Insufficient description of which adverse effects were observed. | Nurse from a different institute | – | No description | No information | ! | Described as time spend for catheter insertion in minutes. No further description. | No information | ! |

Overall RoB 2: Cochrane Risk of Bias 2 overall risk-of-bias judgement for the outcome.[12]
Judgement of the individual domains and answers to signaling questions will be made available upon request to the corresponding author.

Supplementary Table S1 continues on next page

## Supplementary Table S1 continue

| | Osmolality | | | Volume of fluid infused | | | Agitation | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study & year** Country | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 | Method of measuring the outcome | Methods of ascertainment | Overall RoB 2 |
| **Delamaire 1992 France** | | | | | | | | | |
| **Challiner 1994 United Kingdom** | mOsm/kg, Freezing point measurement | Blood samples | – | | | | | | |
| **O'Keeffe 1996 United Kingdom** | | | | ml of fluid infused over 48 hours | Assessed by nursing staff | ! | Presence yes or no | Doctors using Modified Cohen-Mansfield Agitation inventory | ! |
| **Luk 2008 China** | | | | | | | | | |
| **Slesak 2003 Germany** | | | | ml of fluid infused per day | No information | ! | | | |
| **Noriega 2014 Spain** | mOsm/kg | Blood samples | ! | ml of fluid infused per day | Assessed daily by researchers | ! | Presence yes or no | Need for physical / pharmacological restraint. No information on who assessed this. | ! |
| **Esmeray 2018 Turkey** | | | | | | | Presence yes or no | Described as presence of agitation. Assessed by a nurse. | ! |

Overall RoB 2: Cochrane Risk of Bias 2 overall risk-of-bias judgement for the outcome.[12]
Judgement of the individual domains and answers to signaling questions will be made available upon request to the corresponding author.

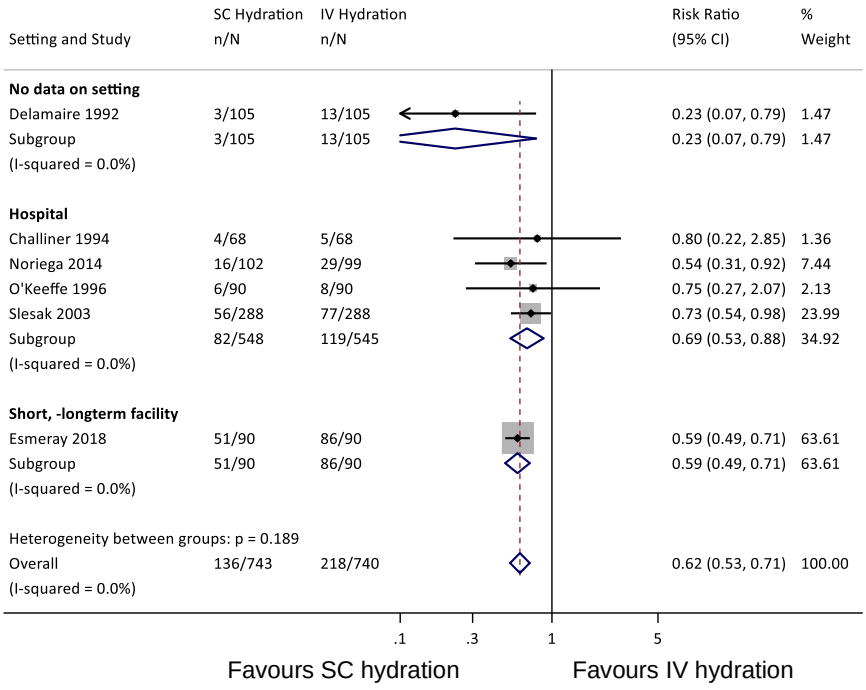
## Supplementary Table S2. Risk of bias of cross-sectional studies for the outcome of adverse effects

| Study<br>(Overall risk of bias) | Appropriate eligibility criteria and recruitment of patients | Lost to follow up | Outcome measure[a] |
|---|---|---|---|
| **Prospective studies** | | | |
| Fainsinger 1994<br>*(High risk of bias)* | *Inadequate* | *Adequate* | *Inadequate* |
| Worobec 1997<br>*(High risk of bias)* | *Adequate* | *Unclear* | *Inadequate* |
| Centeno 1999<br>*(High risk of bias)* | *Adequate* | *Unclear* | *Inadequate* |
| Torsheim 1999<br>*(Low risk of bias)* | *Adequate* | *Adequate* | *Adequate* |
| Dasgupta 2000<br>*(Low risk of bias)* | *Adequate* | *Adequate* | *Adequate* |
| Arinzon 2004<br>*(Low risk of bias)* | *Adequate* | *Adequate* | *Adequate* |
| Lamandé 2004<br>*(Low risk of bias)* | *Adequate* | *Adequate* | *Unclear* |
| Martinez-Riquelme 2005<br>*(High risk of bias)* | *Unclear* | *Unclear* | *Inadequate* |
| Stastna 2009<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Bigot 2013<br>*(High risk of bias)* | *Unclear* | *Unclear* | *Inadequate* |
| Justino 2013<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Vidal 2016<br>*(High risk of bias)* | *Adequate* | *Inadequate* | *Unclear* |
| **Retrospective studies**[b] | | | |
| Schen 1981<br>Schen 1982<br>Schen 1983<br>*(High risk of bias)* | *Unclear* | *Adequate* | *Inadequate* |
| Bruera 1990<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Bruera 1996<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Hussain 1996<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Yap 2001<br>*(High risk of bias)* | *Adequate* | *Adequate* | *Inadequate* |
| Chalany 2015<br>*(High risk of bias)* | *Unclear* | *Adequate* | *Adequate* |

[a]Further information on adverse effects description of included studies will be made available upon request to the corresponding author.
[b]Retrospective studies are judged to have a higher baseline risk of bias by design.

## Supplementary Figure S1. Subgroup meta-analysis by setting of study on number adverse effects comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².




Tests of effect size = 1:

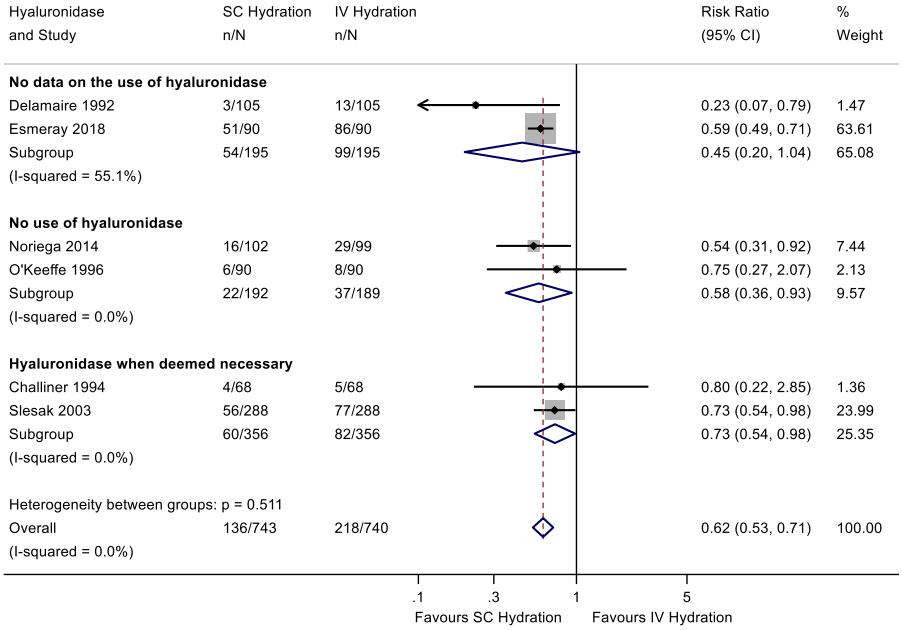
| | |
|---|---|
| No data on setting | z = -2.344 p = 0.019 |
| Hospital | z = -2.950 p = 0.003 |
| Short, -longterm facility | z = -5.504 p > 0.00001 |
| Overall | z = -6.417 p > 0.00001 |

Mantel-Haenszel Q statistics for heterogeneity

| | Value | df | p-value |
|---|---|---|---|
| No data on setting | 0.00 | 0 | . |
| Hospital | 1.02 | 3 | 0.795 |
| Short, -longterm facility | 0.00 | 0 | . |
| Overall | 4.36 | 5 | 0.499 |
| Between | 3.33 | 2 | 0.189 |
| Between:Within (F) | 4.88 | 2, 3 | 0.114 |

## Supplementary Figure S2. Subgroup meta-analysis by use of hyaluronidase on number adverse effects comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².




Tests of effect size = 1:

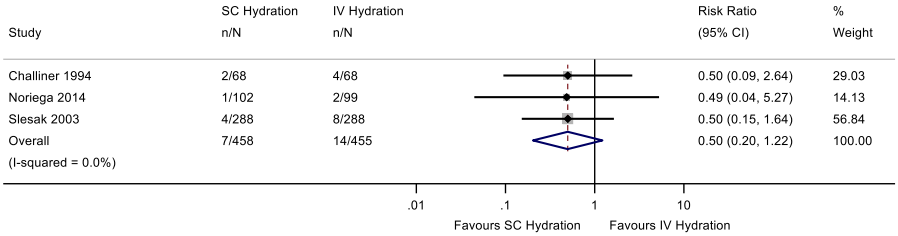
| | |
|---|---|
| No data on the use of hyaluronidase | z = -1.858 p = 0.063 |
| No use of hyaluronidase | z = -2.245 p = 0.025 |
| Hyaluronidase when deemed necessary | z = -2.084 p = 0.037 |
| Overall | z = -6.417 p > 0.00001 |

Mantel-Haenszel Q statistics for heterogeneity

| | Value | df | p-value |
|---|---|---|---|
| No data on the use of hyaluronidase | 2.67 | 1 | 0.102 |
| No use of hyaluronidase | 0.33 | 1 | 0.567 |
| Hyaluronidase when deemed necessary | 0.02 | 1 | 0.886 |
| Overall | 4.36 | 5 | 0.499 |
| Between | 1.34 | 2 | 0.511 |
| Between:Within (F) | 0.67 | 2, 3 | 0.576 |

## Supplementary Figure S3. Meta-analysis on serious adverse effects comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².
All studies in this analysis have Some Concern of bias.



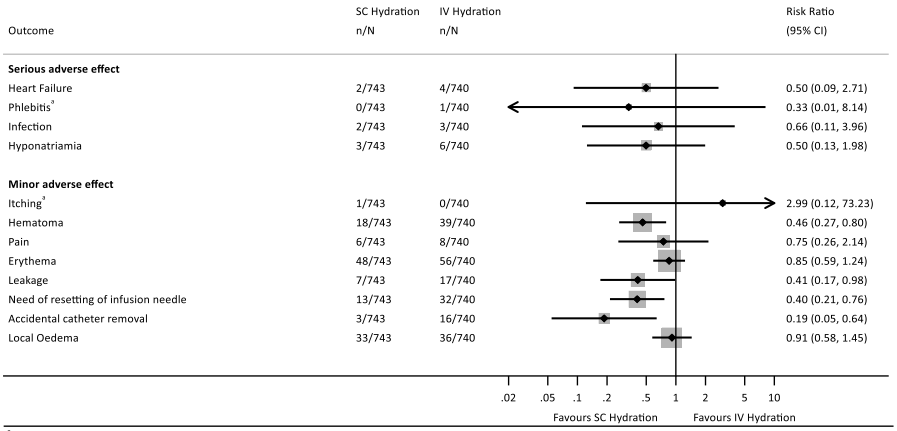

Both-armed zero-event (BA0E) excluded due to the choice of DerSimonian-Laird random effects model.

Test of overall effect = 1: z = -1.525 p = 0.127

Heterogeneity Measures

| | Value | df | p-value |
|---|---|---|---|
| Mantel-Haenszel Q | 0.00 | 2 | 1.000 |
| I² (%) | 0.0% | | |
| Modified H² | 0.000 | | |
| tau² | 0.0000 | | |

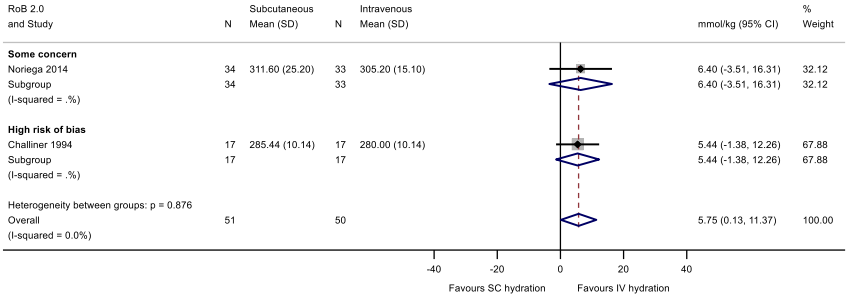
**Supplementary Figure S4. Meta-analysis on all the different types of adverse effects comparing subcutaneous vs intravenous hydration**




[a]Continuity correction of 0.50 applied to studies with zero cells.
n/N: Number of adverse effects / Number of infusions, CI: Confidence Interval, SC: Subcutaneous, IV: Intravenous.

## Supplementary Figure S5. Meta-analysis on reduction of serum osmolality comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Mean Differences using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².




Tests of effect size = 0:

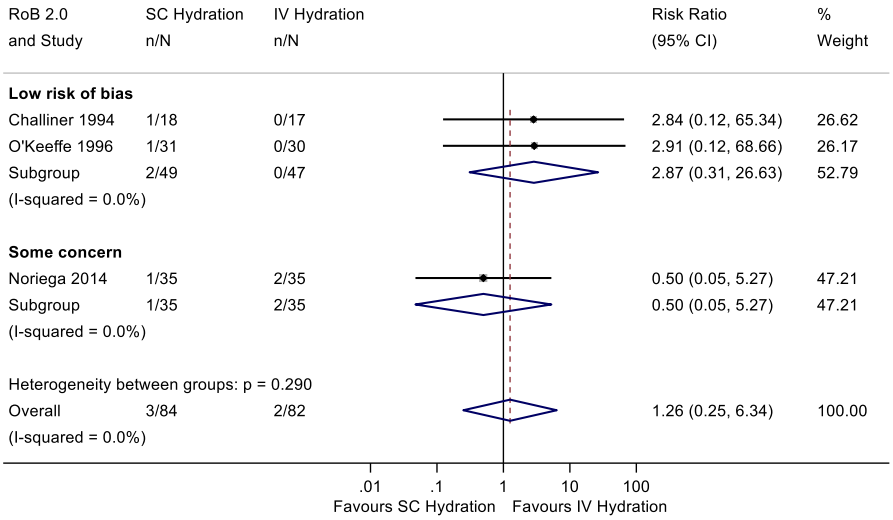
| | | |
|---|---|---|
| Some concern | z = 1.265 | p = 0.206 |
| High risk of bias | z = 1.563 | p = 0.118 |
| Overall | z = 2.005 | p = 0.045 |

Cochran Q statistics for heterogeneity

| | Value | df | p-value |
|---|---|---|---|
| Some concern | 0.00 | 0 | . |
| High risk of bias | 0.00 | 0 | . |
| Overall | 0.02 | 1 | 0.876 |
| Between | 0.02 | 1 | 0.876 |
| Between:Within (F) | . | 1, 0 | . |

## Supplementary Figure S6. Meta-analysis on death comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².




Both-armed zero-event (BA0E) excluded due to choice of DerSimonian-Laird for estimating tau-squared. Continuity correction of 0.50 applied to studies with zero cells.

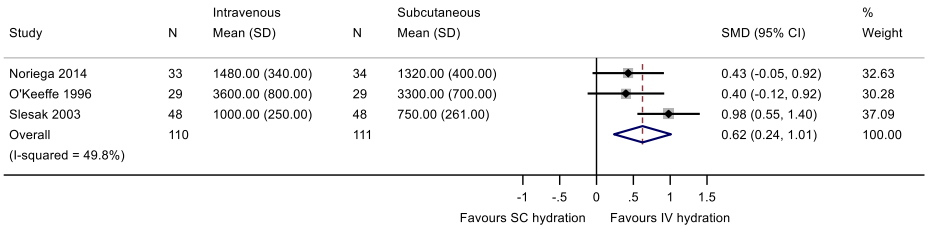
Tests of effect size = 1:
Low risk of bias z = 0.929 p = 0.353
Some concern z = -0.577 p = 0.564
Overall z = 0.279 p = 0.780

Mantel-Haenszel Q statistics for heterogeneity

| | Value | df | p-value |
|---|---|---|---|
| Low risk of bias | 0.00 | 1 | 0.992 |
| Some concern | 0.00 | 0 | . |
| Overall | 1.12 | 2 | 0.571 |
| Between | 1.12 | 1 | 0.290 |
| Between:Within (F) | 11611.40 | 1, 1 | 0.006 |

## Supplementary Figure S7. Meta-analysis on volume of fluid infused comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Standardised Mean Differences by the method of Cohen using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².
All studies in this analysis have Some Concern of bias.



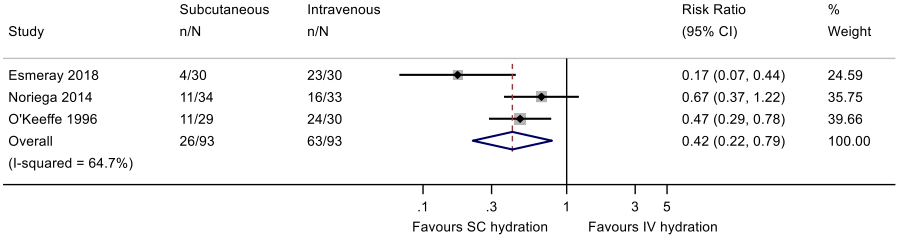

Test of overall effect = 0: z = 3.163 p = 0.002

Heterogeneity Measures

| | Value | df | p-value |
|---|---|---|---|
| Cochran's Q | 3.99 | 2 | 0.136 |
| I² (%) | 49.8% | | |
| Modified H² | 0.993 | | |
| tau² | 0.0582 | | |

## Supplementary Figure S8. Meta-analysis on agitation comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².
All studies in this analysis have Some Concern of bias.



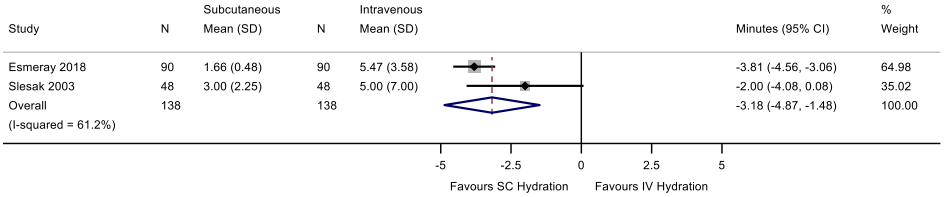

Test of overall effect = 1: z = -2.689 p = 0.007

Heterogeneity Measures

| | Value | df | p-value |
|---|---|---|---|
| Mantel-Haenszel Q | 6.03 | 2 | 0.049 |
| I² (%) | 64.7% | | |
| Modified H² | 1.831 | | |
| tau² | 0.1996 | | |

## Supplementary Figure S9. Meta-analyses on time spend on catheter insertion comparing subcutaneous vs intravenous hydration

Meta-analysis pooling of Mean Differences using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau².
All studies in this analysis have Some Concern of bias.

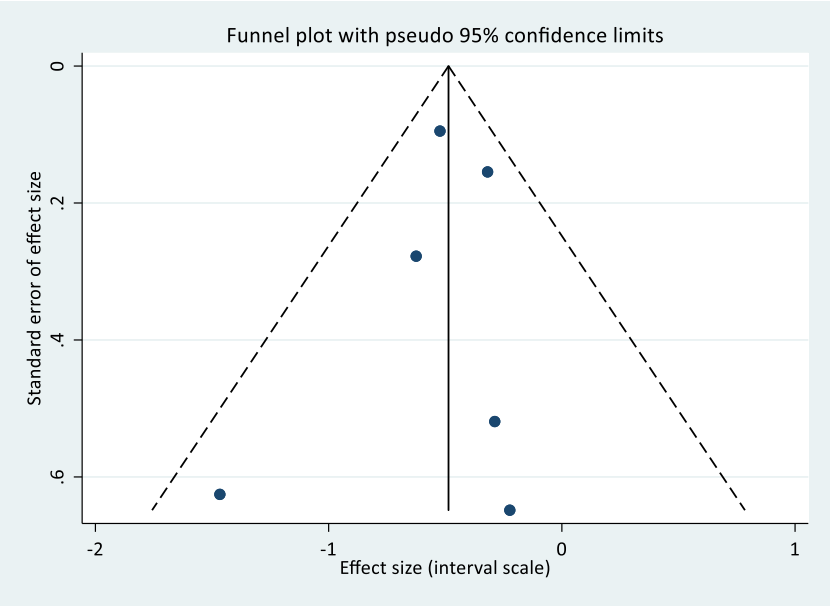



Test of overall effect = 0: z = -3.678 p = 0.00012

Heterogeneity Measures

| | Value | df | p-value |
|---|---|---|---|
| Cochran's Q | 2.58 | 1 | 0.108 |
| I² (%) | 61.2% | | |
| Modified H² | 1.577 | | |
| tau² | 1.0024 | | |

**Supplementary Figure S10. Funnel plot for adverse effects from 6 RCTs of subcutaneous vs intravenous hydration**



## Supplementary Table S3. GRADE Evidence profile: subcutaneous hydration

| Quality assessment | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Adverse effects / number of infusions | | | Absolute risk per 1000 infusions | | |
| No of studies (design) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | SC | IV | Risk Ratio (95% CI) | Incidence of adverse effects with SC hydration | Incidence of adverse effects with SC hydration | Quality |
| Risk of adverse effects | | | | | | | | | | | |
| Lowest risk of bias subgroup (4 RCTs) | Serious limitations[a] | No inconsistency | No serious indirectness | Serious imprecision[b] | Undetected | 82/548 | 119/545 | RR 0.69 (0.53: 0.88) | 90[c] | 130 with IV (95% CI 102-169)[d] | ⨁⨁⨁O Moderate |
| | | | | | | n (SC) | n (IV) | Effect measure (95% CI) | Absolute effect | | |
| Effect of treating the problem (dehydration), inferred from the surrogate outcome "Effect on serum osmolality" | | | | | | | | | | | |
| (2 RCTs) | Serious limitations[e] | No serious inconsistency | Very serious indirectness | Serious imprecision | Undetected | 51 | 50 | MD 5.75 (0.13: 11.37) | IV hydration will lower serum osmolality by 5.75 mmol/kg (95% CI 0.13 more to 11.4 more) compared with SC hydration. | | ⨁OOO Very low |
| Effect of hydration treatment, "Death" | | | | | | n/N | n/N | | | | |
| (3 RCTs) | No serious limitations | No serious inconsistency | No indirectness | Very serious imprecision | Undetected | 3/84 | 2/82 | RR 1.3 (0.25: 6.34) | Unable to calculate meaningful absolute values due to a very large confidence interval. | | ⨁OOO Very low |
| Effect of the hydration treatment, inferred from the surrogate outcome "Volume of fluid infused" | | | | | | | | | | | |
| (3 RCTs) | Serious limitations[a] | No serious inconsistency | Very serious indirectness | No serious imprecision | Undetected | 110 | 111 | SMD: 0.62 (0.24: 1.01)[f] | IV hydration will infuse 155 ml more fluid per day (95% CI 60 ml more to 253 ml more) compared to SC hydration when infusing 1000 ml/day.[g] | | ⨁OOO Very low |
| Effect of the hydration treatment, inferred from the surrogate outcome "Agitation" | | | | | | n/N | n/N | | | | |
| (3 RCTs)[h] | Serious limitations[a] | No serious inconsistency | Serious indirectness | No serious imprecision | Undetected | 26/93 | 63/93 | RR 0.42 (0.22: 0.79) | 68% of patients with some cognitive impairment treated with IV hydration experience agitation vs 28% treated with SC hydration (95% CI 15-54). | | ⨁⨁OO Low |

Table S3 continued

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time spent on catheter insertion | | | | | | | | | | |
| (2 RCTs) | Serious limitations[a] | Serious inconsistency | No serious indirectness | No serious imprecision | Undetected | 138 | 138 | MD 3.2 (1.48: 4.87) | Setting up SC hydration takes 3.2 fewer minutes (1.5 to 4.9 less) than setting up IV hydration. | ⨁OOO Very low |

RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, CI: Confidence interval, RR: risk ratio, MD: Mean difference, SDM, Standardized Mean Difference.

[a] All studies at Some Concern of bias.

[b] Optimal information size not reached (740 infusions needed in both groups).

[c] Based on incidence of adverse effects from SC hydration from the studies with the lowest risk of bias (4 RCTs and 4 observational studies.)

[d] Calculated by multiplying the incidence with SC hydration with the inverse risk ratio from the meta-analysis.

[e] One study with some concern and one with high risk of bias.

[f] We have use standard mean difference (SMD) as included studies reported either volume per day or volume overall.

[g] Based on numbers from Slesak 2003[29] with 1000 ml ± 250 being infused per day in IV group.

[h] All studies included mostly patients with cognitive impairment or dementia.

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# Appendix B. Study II

## Adverse effects of subcutaneous vs. intravenous hydration on older adults: An assessor-blinded RCT

### Running title: RCT on Hydration in Older Patients

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This is the submitted version of the study. Citation of the published study:
Danielsen, M. B., Worthington, E., Karmisholt, J. S., Møller, J. M., Jørgensen, M. G., & Andersen, S. (2022). Adverse effects of subcutaneous vs intravenous hydration in older adults: An assessor-blinded randomised controlled trial (RCT). Age and Ageing, 51(1). https://doi.org/10.1093/ageing/afab193

## Abstract

**Background**
Hydration therapy is essential in the care of the older patient. Subcutaneous (SC) hydration is a relevant method for parenteral hydration, but clinical trials on the subject have methodological shortcomings compared to updated standard.

**Design**
We performed an assessor-blinded, non-inferior trial to explore if SC is a safe alternative to intravenous (IV) hydration and to advance the quality of literature on the subject.

**Participants**
Eligibility patients were: Older adults 65 years or older with a need for parenteral hydration admitted to an acute assessment unit, an orthopedic ward with hip fracture or a short-term care facility. The targeted sample size was 67 patients in each group.

**Intervention:**
Patients were randomized to receive parenteral hydration either via an IV or SC placed catheter during a 24 hours observation period. The non-randomized catheter was placed as a sham on the patient, thereby blinding the caregivers and outcome assessors.

**Measurement**
Our primary outcome was the proportion of patients reporting at least one adverse effect with a non-inferior calculation using a 20% margin.

**Results**
We included 51 patients with 24 randomized to SC and 27 to IV. The number of included patients were restricted by a time limitation and COVID-19. For the outcome of adverse effects, SC was found to be non-inferior to IV ($p = 0.012$). Time spent on inserting the catheters was significantly shorter with SC ($p=0.001$). However, there was no difference between the groups on pain of insertion, discomfort during infusion, or the risk of developing delirium.

**Conclusion**
SC is a safe alternative to IV hydration, is faster to place and should be an available method for parenteral hydration wherever older adults are cared for.

Trial registration: ClinicalTrials.gov Identifier: NCT03710408
**Primary funding source:** No external funding


Key Words: Hypodermoclysis, Older patients, Hydration treatment, randomized controlled trial, non-inferior, assessor blinding

## Introduction

Adequate hydration is essential in the treatment of older patients as dehydration is a common and potentially dangerous condition in our patient group.[3,5,11] There are two main methods for parenteral hydration; intravenous (IV) is a common choice, but subcutaneous (SC) hydration is an alternative that deserves further attention. Our recent comprehensive systematic review reported a limited number of randomized controlled trials on the subject[56] that were conducted and reported before the introduction of current guidelines, leading to several methodological shortcomings.[41,42,46,70,71,73] As a method of parenteral hydration, SC has potential advantages compared to IV as the literature suggests fewer adverse effects with subcutaneous hydration than with IV. However, none of the previous trials had blinded outcome assessors or were registered with a description of outcomes, limiting the validity of their results. Furthermore, it may be faster to place the SC catheters than the IV catheters, but this result had a high risk of bias. Finally, the risk of delirium may be lower when using SC hydration compared to IV.[56]

The limitation of previous trials on the subject led us to perform a randomized controlled trial (RCT) comparing SC with IV hydration. Our trial adheres to current methodological guidelines, including blinding of the outcome assessors to strengthen the quality of the literature on the subject. A concern for adverse effects was raised by other healthcare professionals when we introduced SC as a method for hydration, and thus our trial's main outcome is the risk of adverse effects. We aimed to investigate if SC hydration is a relevant alternative to IV, rather than if it should replace IV. Hence, the non-inferiority design. Our RCT use a non-inferiority margin of 20%. This means that the proportion of patients experiencing a minor adverse effect in the SC group must not exceed an upper limit of 20% above the proportion reported in the IV group. This margin was settled based on a protocol for a Cochrane review on achieving access for hydration[64] and through discussions with consultants in geriatric medicine.

Additional outcomes were the time spent on inserting the catheters, the patient's experience of insertion and infusion of fluid, and the risk of developing delirium. We included older adults with mild dehydration or at risk of dehydration during either an admission to hospital or short-term care.

## Methods

### Trial design

This trial was a randomized controlled, parallel-group, assessor-blinded, non-inferior trial registered on ClinicalTrials.gov (NCT03710408). The reporting follows the CONSORT guidelines[51] with the harms[63] and non-inferior extensions.[65] Ethical approval was granted by the local Committee on Health Research Ethics (Project ID: N–20180014) in the North Denmark Region.

## Participants

We conducted the trial at Aalborg University Hospital, Denmark, and at a short-term care facility in Aalborg. During the trial the number of locations was increased during the trial to enhance recruitment. The inclusion criteria' for the trial were: age 65 years or older, a prescription of 1-2 liters of parenteral fluid over the next 24 hours (mild dehydration or at risk of dehydration), and admission to either acute assessment unit, an orthopedic ward with a hip fracture, or admission to a short-term care facility. Exclusion criteria' were: Severe dehydration (expected to need more than 2 L of parenteral fluid over the next 24 hours), fluid restriction, unable to give informed consent, severe general edema, or planned discharge from the hospital or care facility within the next 24 hours. Patients were only allowed to receive parenteral fluid through the trial setup but were encouraged to drink fluid; IV medication, such as antibiotics, were allowed using a different IV access.

## Interventions

A member of the author group assessed eligibility, obtained informed consent, and enrolled patients. Baseline measurements were obtained before randomization, and eligible patients were randomized in the ratio of 1:1 to receive parenteral fluid through either an IV or SC placed catheter. The IV catheters were "BD Venflon™ Pro Safety – 22G (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA)" placed in a vein on the dorsal side of the hand or forearm. The SC catheters were "BD Saf-T-Intima™ - 22G (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA)" (butterfly needle with a plastic catheter) placed in the lower right or left quadrant of the abdomen. A sham catheter not piercing the skin was placed on the non-randomized location to achieve blinding of the care personnel and outcome assessors. A small non-transparent gauze square was placed on top of both the randomized and non-randomized catheter to hide whether the catheter pierced the skin. Infusion lines primed with infusion fluid were connected to both the catheters and the line connected to the randomized catheter was inserted into a fluid bag. The infusion lines were intertwined, and this entanglement was covered with opaque fabric. This setup prevented the outcome assessors from knowing which catheter had pierced the skin of the patient. A more detailed description and a graphical representation of the trial intervention setup can be found in the supplementary. The fluid flow rate was roughly 3 ml per minute, and a liter of fluid was infused in 6 to 8 hours. The setup allowed the nursing staff to change the infusion bag and flow speed without knowing the patient's randomization.

## Primary outcome

The primary outcome of this trial was the risk of adverse effects. The Cochrane handbook[114] defines an adverse effect as "An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility." We observed patients for the following minor adverse effects: reddening of the skin at the insertion site, painful swelling, itching, phlebitis, infusion-related pain,

termination of flow, need for reinsertion of the catheter, accidental catheter removal by the patient, need for a reduction of flow speed, and prolong swelling at the infusion site (>2 hours). Short-term swelling without discomfort was not recorded as an adverse effect. Both during and after the observation period, the patient's charts were inspected for signs of severe adverse effects such as pulmonary edema, cardiac failure, hyper/hyponatremia, and infection at the insertion site. The patients were observed for 24 hours. We chose this short observation period to reduce the risk of violating the blinding and patients changing treatment groups. Outcome assessors were the nursing staff at the locations, and they recorded adverse effects three times during the 24 hours observation period.

**Secondary outcomes**

Secondary objectives were the presence of delirium based on the Confusion Assessment Method (CAM)[66] at the end of the observation period and whether the patient died during admission. Also, the patients were asked to evaluate the pain of insertion of the randomized catheter and the discomfort of the infusion of fluid using a VAS from 0-100. Finally, the time spent on inserting the randomized catheter was recorded in categories 1 to 6 (1: less than three minutes, 2: 3 to 5 minutes, 3: 5 to 10 minutes, 4: 10 to 20 minutes, 5: need assistance from another staff, 6: need assistance from an intensive care nurse). Categorization was chosen over a continuous recording of time to allow for the two latter groups to be included. Biochemical markers of hydration (hemoglobin, sodium, potassium, urea nitrogen, creatinine, osmolality, albumin, eGFR (CKD-EPI[115]) were collected at the beginning and the end of the 24 hours observation period.

**Sample size**

Our sample size calculation was based on previous trials on this topic with a short observation time (less than 48 hours). They reported an incidence of adverse effects of 17% in both the SC and IV groups.[41,42] With a significance level of 5%, a power of 90%, and a non-inferior limit of 20%, a non-inferiority sample size calculation with a binary outcome resulted in 61 participants required in each group.[116] We expected an attrition rate of 10%, giving us a sample size of 67 patients in each group.

**Randomization**

The included patients were randomized after baseline measurements via a webform using REDCap version 7.0.11 hosted at Aalborg University Hospital[117]. A REDCap data manager generated the randomization sequence as a block randomization with unknown block sizes.

**Statistical analysis**

Before the completion of recruitment and any data analysis, a statistical analysis plan was made with a biostatistician's support and uploaded to clinicaltrials.gov

NCT03710408. All analyses were performed with an intention-to-treat approach. For the primary outcome (dichotomous, blinded, non-inferior), a one-sided z-test for non-inferiority was used.[67] If the primary outcome was found to be significantly non-inferior, we performed a superiority test (Fisher's exact test).

For further analyses of the primary outcome, counting all adverse effects, not just the first (discrete, non-inferior), we used a Wilcoxon rank-sum test. All further analyses are superior analyses. Dichotomous and ordered categorical data will be analyzed with a Fisher's exact test and discrete data with a t-test.

Groups are collapsed if there are fewer than 1 or multiple groups with fewer than 5 patients. Biochemical markers of hydration are displayed as mean + SD at baseline, endpoint, and change and presented in supplementary table S1. Statistical tests on the biochemical markers of hydration are not performed due to the risk of multiple comparison error (type one error) and the indirectness of these markers on the outcome of hydration status. All statistical analyses were performed by MBD, who was blinded to intervention group allocation during data analysis. All analyses were done using STATA 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.)

**Table 1. Baseline data of included patients**

| | | SC group | IV group |
|---|---|---|---|
| Age | | 79 (7.3) | 83 (6.9) |
| Sex (female)[a] | | 16 (66%) | 17 (62%) |
| Site of recruitment[a] | ER: | 7 (29%) | 7 (26%) |
| | Orto: | 14 (58%) | 18 (67%) |
| | Short-term: | 3 (13%) | 2 (7%) |
| Number of known comorbidities | | 4.6 (1.9) | 3.9 (1.4) |
| Charlson Comorbidity Index[94] Median (25-75 range) | | 1 (0-2) | 0 (0-2) |
| Treated with anti-coagulant medication[a] | | 8 (35%) | 9 (33%) |
| Systolic Blood Pressure (mm Hg) | | 136 (28) | 129 (21) |
| Diastolic blood Pressure (mm Hg) | | 68 (10) | 69 (12) |
| Pulse (/min) | | 83 (18) | 79 (12) |
| Hemoglobin (g/dl)[b] | | 10.5 (2.3) | 11.3 (2.5) |
| Sodium (mEq/l) | | 137 (3.5) | 137 (3.7) |
| Potassium (mEq/l) | | 3.8 (0.6) | 3.8 (0.6) |
| Urea (mg/dl)[c] | | 50 (25) | 56 (46) |
| Creatinine (mg/dl)[d] | | 1.1 (0.46) | 1.0 (0.46) |
| eGFR (ml/min/1.73m$^2$) | | 61 (23) | 63 (24) |
| Albumin (g/dl)[e] | | 2.7 (0.38) | 2.9 (0.43) |
| Osmolality (mmol/kg) | | 294 (18) | 290 (11) |

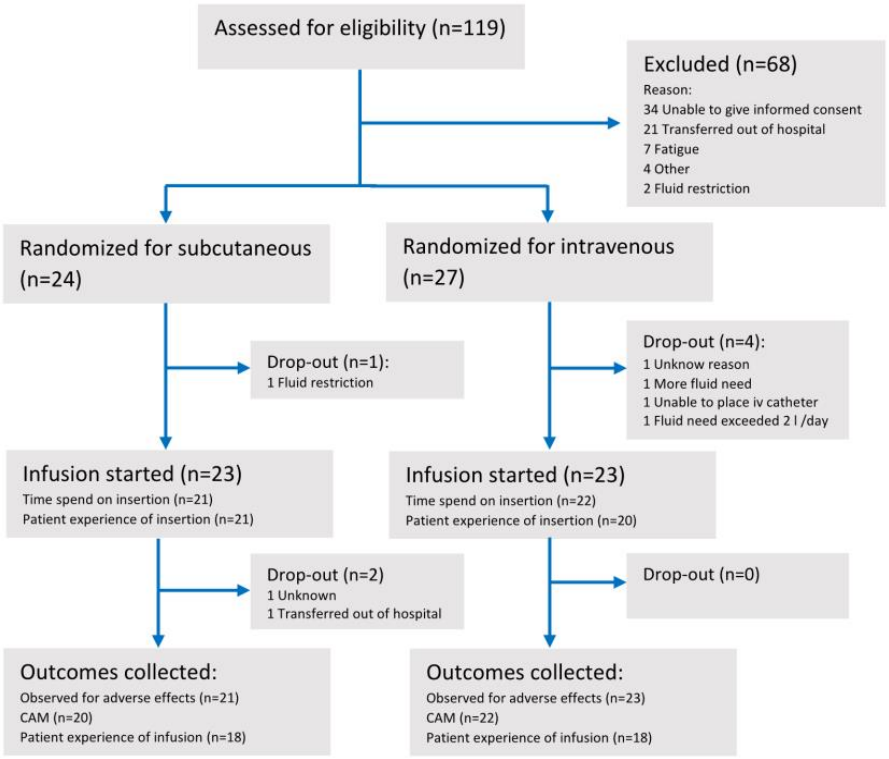
Abbreviations: ER: Emergency room, Orto: Orthopedic ward;
Unless otherwise indicated, data are expressed as mean (standard deviation)
[a]Data expressed as number (percent), [b]To convert the values for hemoglobin to mmol/l multiply by 0.62, [c]To convert the values for urea to mmol/ divide by 6, [d]To convert the values for creatinine to µmol/l multiply by 88.42, [e]To convert the values of albumin to g/l multiply by 10.

## Results

We screened patients for eligibility from January 2019 to November 2020, and we assessed 119 patients, and 51 were eligible and accepted inclusion, while 68 were excluded. Most of the exclusions were due to the inability to give informed consent. Twenty-four of the included patients were randomized for SC and 27 for IV. The discrepancy between the numbers recruited in the two groups is due to ending the recruitment in the middle of a randomization block. Due to the workflow, we do not know the exact number of potentially eligible patients. See figure 1 for the flow of patients.

Of the 51 patients randomized, 14 patients were recruited at the acute assessment unit, 32 from the orthopedic ward, and five from the short-term care facility. The trial was terminated before reaching the sample size target due to the trial's time restriction, and due to the restrictions imposed by the COVID-19 pandemic. The principal admission diagnosis was a hip fracture followed by dehydration.

**Figure 1.** Flow diagram of patients



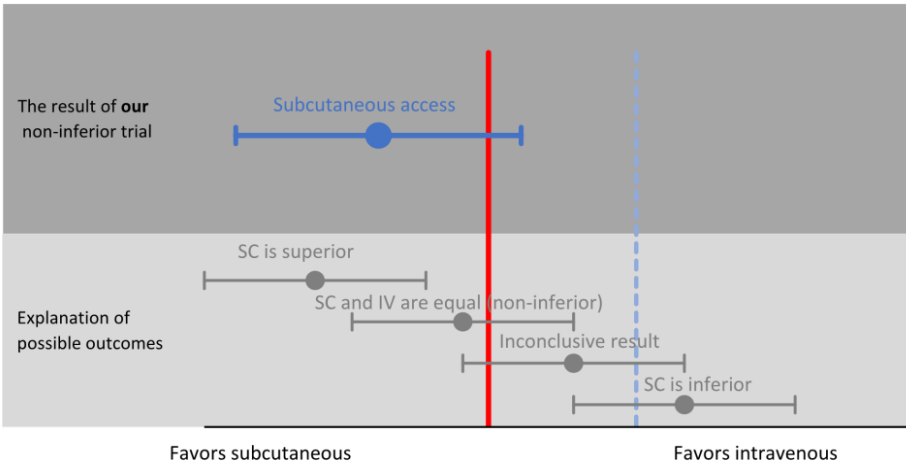

Abbreviations: CAM: Confusion Assessment Method[66]

The mean age of the included patients was 79 (SD 7.3) years in the subcutaneous group and 83 (SD 6.8) years in the IV group. The included patients had an average of 4 comorbidities, were all mildly dehydrated or at risk of dehydration, and received one liter of parenteral fluid during the trial period of 24 hours. See all baseline data in table 1.

At termination of the trial, 21 patients in the SC group and 23 in the IV group had completed the observation for adverse effects. No participant had a serious adverse effect, changed their treatment group during the observation period, or left the trial because of adverse effects. Six (28%) and 10 (43%) patients experienced at least one adverse effect in the SC and IV groups, respectively. Our primary outcome of adverse effect (non-inferior, blinded outcome assessor) showed that SC was significantly non-inferior to IV (p=0.012) (figure 2). Post hoc power analysis of the primary outcome showed a power of 77%.

A superiority calculation of adverse effects shows that SC is not significantly superior to IV with a risk ratio of 0.66 (95% CI: 0.29 – 1.49, p = 0.36). When including all reported adverse effects, and not just the first, SC was still not superior to IV (p=0.19). There were no reports of bleeding or hematoma related to the catheters during the observation, and no patient died during their admission. See supplementary figure S2 for details of the observed adverse effects.

**Figure 2.** Graphical presentation of the non-inferiority of subcutaneous vs. intravenous hydration.




Footnote: The solid red line represents the line of no difference between subcutaneous (SC) and intravenous (IV). The dashed blue line represents our pre-specified non-inferiority margin. p-value for non-inferiority = 0.012. The risk ratio between subcutaneous and intravenous is RR 0.66 (95% CI 0.29-

When patients experienced an adverse effect that caused the infusion to stop, it was assessed by the nursing staff if the patient needed to complete the hydration treatment or had received sufficient fluid. This is the reason for the discrepancy between the number of terminated flow and accidental catheter removal by the patients and the number of reinsertions reported.

SC catheters were significantly faster to place than IV (p = 0.001, table 2, supplementary figure S3). Most SC catheters took less than five minutes to place, where the placement of IV catheters often took longer. Three patients in the IV group had delirium at the end of observation compared to 0 in the SC group (p = 0.23). The patients randomized to IV reported a mean pain score for insertion of catheter of 13.0 (SD 13.4) compared to 7.3 (SD 10.4) in the SC group on a scale from 0-100 (p = 0.13). Mean reported discomfort during infusion was 4.7 (SD 7.5) and 4.5 (SD 11.8) in the IV and SC group, respectively, again on a scale from 0-100 (p = 0.74). All secondary outcomes are reported in table 2.

**Table 2.** Secondary outcomes

| Outcome | Subcutaneous group n(%) | Intravenous group n(%) | Difference (95% CI) | p-value for difference |
|---|---|---|---|---|
| Time spend on insertion[a] | < 5 min: 18 (85%)<br>5-20 min: 2 (10%)<br>> 20 min[b]: 1 (5%) | 7 (32%)<br>9 (41%)<br>6 (27%) | N/A | 0.001 |
| Death during hospitalization | 0 (0%) | 0 (0%) | N/A | N/A |
| Delirium | 0 (0%) | 3 (14%) | | 0.23 |
| | **n, mean (SD)** | **n, mean (SD)** | | |
| Pain of insertion (0-100 VAS) | n=21, 7.3 (10.4) | n=20, 13.0 (13.4) | 5.7 (-1.9; 13.2) | 0.13 |
| Discomfort during infusion (0-100 VAS) | n=18, 4.5 (11.8) | n=18, 4.7 (7.5) | 0.2 (-6.9; 4.5) | 0.74 |

Abbreviations: VAS: Visual analog score, N/A: Not applicable

[a]Original groups are collapsed due to the low number of events in some groups.

[b]Requiring assistance from another staff member

## Discussion

We performed an assessor-blinded, non-inferiority, RCT, adhering to current guidelines, including trial registration and uploading of the statistical analysis plan. Our primary outcome of adverse effects showed that SC hydration was non-inferior to IV. Furthermore, the time it took to place an SC catheter was significantly shorter than placing an IV catheter.

Our trial was successful in its aim, providing high-quality evidence that subcutaneous hydration appears to be a safe alternative to IV. The incidence of adverse effects in our trial was higher than reported in other trials on SC hydration.[41,42,46,73] This could be due to our scrutinizing observation for adverse effects since this was our primary outcome. Both IV and SC hydration appear to be safe methods for hydration as we found no serious adverse effects, and the main adverse effects reported were minor nuisances such as termination of flow and accidental catheter removal by the patient.

A low number of patients developed delirium during the observation period with zero in the SC group and three in the IV group. However, this was expected as one of the inclusion criteria were: "being able to provide informed consent". The non-significant difference in risk of delirium between groups is in contrast with the findings in our recent systematic review. Here we found a reduced risk of agitation in patients receiving subcutaneous hydration.[56] However, the trials on this outcome included patients with cognitive impairment, being more vulnerable patients than those included in our trial.[42,71,73]

We found that that SC catheters were significantly faster to place than IV, which is in line with the findings reported in our systematic review, and our results raise the confidence in this estimate. In general, patients reported minimal discomfort from placement of the catheters and discomfort during the infusion. This conforms to findings by a previous trial that showed the patient had a mean discomfort score of 2 on a 6 pointer Likert-like scale.[46]

## Limitations

A major limitation of our trial is the intended sample size and the actual sample size. Nonetheless it is intriguing that our main result still was statistically significant despite this shortcoming. Furthermore, many patients were not eligible due to an inability to provide informed consent. These vulnerable individuals are frequent visitors to hospitals and short-term care facilities, and their absence lowers the external validity of our results.

Our observation period of 24 hours is shorter than the average duration of parenteral catheters. This observation time was chosen primarily to reduce the risk of violation of the blinding, and secondly to prevent cross-over of patients between randomization groups. The latter violation was reported by previous trials, in which a large proportion of patients swapped group during the trial and thus blurring the interpretation of results.[46]

The main strengths of our trial are the registration with description of all outcomes prior to inclusion of the first patient, and registration of a detailed statistical analysis plan. These factors reduce the risk of bias of selective outcome reporting. Furthermore, the blinding of the outcome assessor reduces the risk of bias in our

primary outcome. These factors contribute to a raised confidence in the estimates and strengthen the recommendation to use SC hydration.

In conclusion, SC hydration is non-inferior to IV for the outcome of adverse effects, and no serious adverse effects were reported. The overall discomfort was minimal from both hydration treatments, but SC catheters were significantly faster to place than IV. Based on our results clinicians should consider SC hydration as an alternative in patient with mild dehydration or at risk of dehydration and maybe even preferred, in patients at risk of delirium.

## Acknowledgments

We would like to thank Kirsten Duch, Msc, Unit of Clinical Biostatistics, Aalborg University Hospital, for statistical assistance. We acknowledge the support of the departments of Geriatric Medicine, Orthopedic Surgery, and Emergency Medicine, Aalborg University Hospital. All who contributed significantly to this work have been mentioned.

**Financial Disclosure**: This trial received no external financial support.

**Conflict of Interest**: No authors have any conflicts of interest.

**Author Contributions:** *Concept and design*: Danielsen, Karmisholt, Jørgensen, Andersen, and Møller.
*Acquisition, analysis, or interpretation of data:* Danielsen, Karmisholt, Jørgensen, Andersen, Worthington, and Møller.
*Drafting of the manuscript:* Danielsen, Andersen.
*Critical revision of the manuscript for important intellectual content:* Danielsen, Karmisholt, Jørgensen, Andersen, Worthington, and Møller.

**Sponsor's Role**: None.

## REPRODUCIBLE RESEARCH STATEMENT

ClinicalTrials.gov registration and statistical analysis plan: NCT03710408
Statistical code and data set: available from M. Danielsen MD, Department of Geriatric Medicine, Aalborg University Hospital, Aalborg, Denmark. E-mail: maad@rn.dk

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## Supplementary to

# Adverse effects of subcutaneous vs. intravenous hydration on older adults: An assessor-blinded RCT

**Supplementary text 1.** Description of the trial setup

1) First the randomized catheter is placed according to local guidelines. Before placing the transparent film dressing (*M3™, Tegaderm™*), a small gauze square (*Abena, Curi-Med, Nonwoven Swabs*) is placed over where the needle pierces the skin.

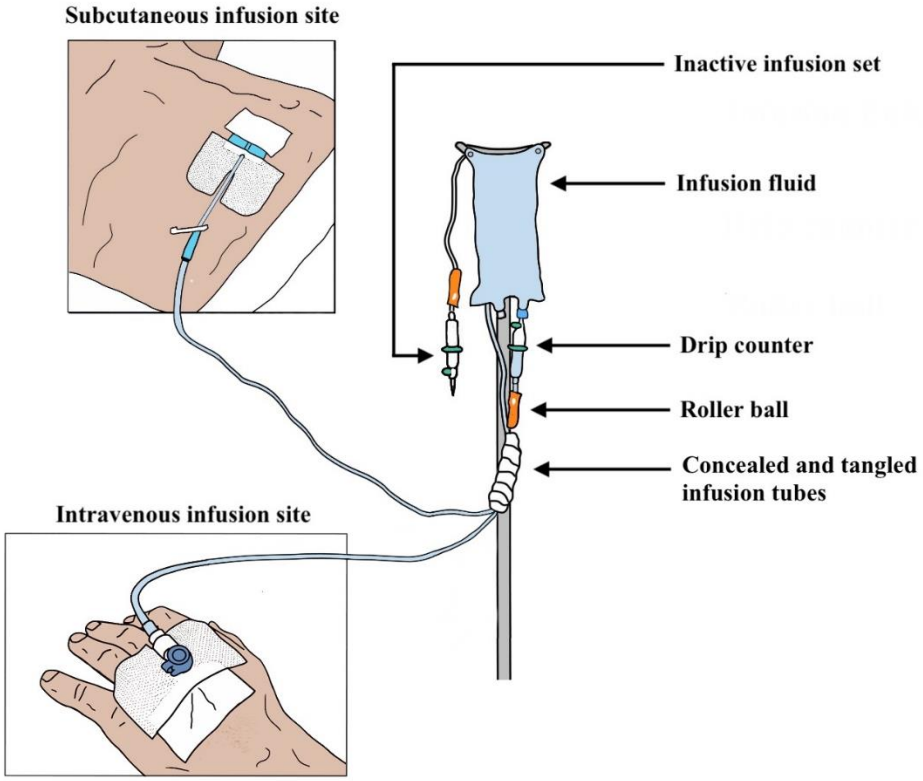
2) The metal needle is removed from the non-randomized catheter and the plastic catheter is shorten with a scissor and placed on top of the skin. A small gauze square is placed covering the plastic catheter before securing the catheter with the transparent film dressing.

3) Two infusion lines (*Braun, Intrafix® SafeSet)* are primed with infusion fluid (Isotonic NaCl) and each of the is connected to each of the catheters. The one connected to the randomized catheter is inserted into the infusion fluid bag.

4) Ensure that the rollerballs are close to the drip counters and intertwined the two infusion lines under the infusion bag. The tangle is secured with tape and covered with fabric.

5) Start the infusion by releasing the rollerball on the infusion line connected to the infusion bag.

**Supplementary figure 1.** Figure showing the trial setup.



**Supplementary table 1.** Markers of hydration status

| | **Baseline** | | **Post intervention** | | **Difference** [a] | |
|---|---|---|---|---|---|---|
| | SC (n=21) | IV (n=25) | SC (n=19) | IV (n=20) | SC (n=19) | IV (n=20) |
| Systolic Blood pressure (mm Hg) | 136 (28) | 129 (21) | 143 (26) | 134 (20) | 5.5 (20.2) | 3.4 (25.2) |
| Diastolic blood pressure (mm Hg) | 68 (10) | 69 (12) | 75 (15) | 72 (7) | 5.1 (13.7) | 1.9 (14) |
| Pulse (/min) | 83 (18) | 79 (12) | 81 (14) | 81 (10) | -1.8 (17) | 2.7 (14) |
| Hemoglobin (g/dl) | 10.5 (2.3) | 11.3 (2.5) | 10.7 (2.3) | 10.3 (1.2) | 0.18 (1.3) | -0.37 (1.2) |
| Sodium (mEq/l) | 137 (3.5) | 137 (3.7) | 138 (3.4) | 137 (4.5) | 1.1 (1.7) | 0.1 (2.6) |
| Potassium (mEq/l) | 3.8 (0.6) | 3.8 (0.6) | 3.7 (0.5) | 3.9 (0.4) | 0.0 (0.3) | 0.0 (0.5) |
| Urea (mg/dl) | 50 (25) | 56 (46) | 47 (23) | 51 (31) | -2.5 (5.8) | 2.1 (16.5) |
| Creatinine (mg/dl) | 1.1 (0.46) | 1.0 (0.46) | 0.8 (0.40) | 0.9 (0.36) | -0.14 (0.23) | -0.03 (0.20) |
| eGFR (ml/min/1.73 $m^2$) | 61 (23) | 63 (24) | 69 (19) | 65 (20) | 3.7 (9.8) | 1.1 (9.7) |
| Albumin (g/dl) | 2.7 (0.38) | 2.9 (0.43) | 2.6 (0.47) | 2.7 (0.36) | -0.18 (0.20) | -0.15 (0.22) |
| Osmolality (mmol/kg) | 294 (18) | 290 (11) | 290 (11) | 290 (11) | 0.3 (8.4) | -0.1 (7.0) |
| Abbreviations: SC: subcutaneous, IV: intravenous,<br>a) Difference is calculated as [post intervention] – [baseline] | | | | | | |

# Appendix C. Study III

## Absorption Rate of Subcutaneously Infused Fluid in Ill Multimorbid Older Patients

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This is the submitted version of the study. Citation of the published study:
Danielsen, M. B., Jødal, L., Riis, J., Karmisholt, J. S., Valdórsson, Ó., Jørgensen, M. G., & Andersen, S. (2022). Absorption rate of subcutaneously infused fluid in ill multimorbid older patients. PloS One, 17(10), e0275783. https://doi.org/10.1371/journal.pone.0275783

## Abstract

### Background

Subcutaneous (SC) hydration is a valuable method for treating dehydration in geriatric patients. Data are absent on the absorption rate and the availability of SC infused fluid in the circulation on this group of patients where SC hydration is particularly relevant.

### Methods

We performed an explorative study on frail, ill octogenarians with comorbidities, who received an SC infusion of 235 ml isotonic saline containing a technetium-99m pertechnetate tracer. The activity over the infusion site was measured using a gamma detector to assess the absorption rate from the SC space. The activity was measured initially every 5 minutes, with intervals extended gradually to 15 minutes. Activity in blood samples and the thyroid was measured to determine the rate of availability in the circulation.

### Results

Six patients were included. The mean age was 81 years (SD 2.1), number of comorbidities was 4.6 (SD 1.3), and Tilburg frailty scale was 3.8 (SD 2.4). When the infusion was completed after 60 minutes, 53% of the infused fluid was absorbed, with 88% absorbed one hour later. The absorption rate from the SC space right after the completion of the infusion was 127 ml/h. Appearance into the blood and the thyroid gland corroborated the transfer from SC to circulation.

### Conclusion

This first study of absorption of SC infused fluid in octogenarians found an acceptable fraction of fluid absorbed from the SC space into the circulation one hour after the end of infusion. Results are uniform but should be interpreted with caution due to sample size.

Trial registration: ClinicalTrials.gov Identifier: NCT04536324

Primary funding source: No external funding

Key Words: Subcutaneous hydration, Hypodermoclysis, Older patients, Hydration treatment, Technetium pertechnetate

## Introduction

Dehydration is a herald of death[3,12], and adequate fluid therapy is an important aspect of treating the older adult. Subcutaneous (SC) hydration is a method for parenteral fluid therapy recommended to treat mild dehydration and patients at risk of dehydration.[56,98] Previous studies have examined the absorption of SC hydration using radioisotopes to track fluid movement in younger adults[118] and healthy adults over 65 years of age.[55,119] The studies found that absorption of the infused fluid was almost complete 60 minutes after the end of the infusion. However, SC hydration therapy is rarely relevant in healthy individuals while it is relevant in dehydrated ill patients who are frail with multiple comorbidities.

With SC hydration, the fluid is absorbed from the SC space into the capillaries through passive diffusion[120], and it has been shown that there is an increased leak from the capillaries during acute illness, potentially reducing their ability to absorb SC infused fluid.[69] Furthermore, albumin is the main osmotic component pulling the fluid into the capillaries.[121] Albumin is often reduced in the ill geriatric patient where SC hydration is relevant either because of acute illness or malnutrition. Both of these physiological changes occur with advanced age and acute illness. However, the influence of these changes on the absorption rate and how complete the absorption is, remains unknown for the ill geriatric patient.

This led us to perform an explorative study in the ill, frail octogenarians admitted to the hospital to estimate the time from infusion to availability in the circulation displayed as a fraction of the infused fluid found in the circulation in a clinically relevant population. We aimed to elucidate when SC hydration could be relevant and potentially guide clinicians in planning the frail older patient's hydration treatment.

## Methods

The study was approved by the local Committee on Health Research Ethics (Project ID: N–20200010) and was registered on Clinicaltrials.gov (NCT04536324). The study was conducted at Aalborg University Hospital, Aalborg, Denmark. The study was initially planned as a case-control study where the primary outcome was the difference between the absorption rate of ill versus non-ill older adults. We only completed the study on ill patients due to time limitations, restrictions from COVID-19 pandemic, and our included patients' frailty. This paper reports all the secondary outcomes planned as registered on Clinicaltrials.gov.

### Participants

We recruited patients admitted to the local geriatric ward as a convenience sample. The study was designed to ensure the recruitment of a population where SC hydration is appropriate to support the study's clinical relevance and external validity.[5]
Inclusion criteria were age above 75 years and ability to give informed consent. This is in accordance with the ethical approval, which unfortunately excludes the delirious

patient, in which SC hydration might be especially useful.[56] Exclusion criteria were: fluid restriction, risk of acute deterioration of illness, and very short life expectancy.
We collected data on the characteristics of the included patients from hospital charts (age, sex, number of prescriptions, number of comorbidities, Charlson Comorbidity Index (CCI)[94]) and through patient interviews (Tilburg Frailty Indicator[95]). Biochemical baseline characteristics recorded were: C-reactive protein, hemoglobin, sodium, potassium, urea nitrogen, creatinine, osmolality, albumin, and eGFR (CKD-EPI[115]). These were obtained by routine analysis at the hospital laboratory on the day of the study procedures.

**Study setup**

We used technetium-99m ($^{99m}$Tc) pertechnetate as a marker for the movement of the infused fluid from the SC space to the circulation as its uptake from SC tissue has been documented to mimic SC water uptake.[55]
We gave the SC infusion through a butterfly needle (BD Saf-T-Intima™ - 22G, Becton, Dickinson, and Company, Franklin Lakes, New Jersey, USA) inserted on the left side of the abdomen, and we collected blood samples through an indwelling intravenous catheter (BD Venflon™ Pro Safety – 18G, Becton, Dickinson, and Company, Franklin Lakes, New Jersey, USA) inserted into the antecubital vein. Patients were infused with 235 ml of isotonic saline. 30 MBq of $^{99m}$Tc were mixed into the infusion fluid before starting the infusion. Mixing pertechnetate into the fluid from the start, rather than using bolus injection(s) at a specific time point(s), ensures that the measured activity is representative of the fluid distribution, even if the uptake rate should be different in the early and late part of the infusion.

After baseline activity measurements were recorded at the insertion site at time 0, we started the SC infusion. The initial speed of infusion was 125 ml/h. The infusion rate was increased to 250 ml/h after 10 minutes if the patients did not experience discomfort. The infusion was completed in 1 hour. During the study, the activity over the infusion site was measured at 5, 10, 15, 20, 30, 40, 50, 60, 70, 85, 100, 115, 130, 145 minutes after the start of infusion by us using a gamma detector (Captus® 3000, Capintec, 7 Vreeland Road, Florham Park, New Jersey, USA). At the same time points, blood samples of 2.7 ml were taken to measure the activity in the circulation. Before extraction of each of these blood samples, 2.7 ml of blood was taken as waste blood.[122] After extracting each of the blood samples, the catheter was rinsed with 5 ml of isotonic saline. Also, pertechnetate activity measurements were performed over the thyroid gland, as pertechnetate is rapidly absorbed by the thyroid gland.[123,124] These measurements were taken from 20 minutes after the start of the infusion and with a similar interval as those taken over the infusion site.

**Method of measurement**

The total dose infused $^{99m}$Tc was measured by a dose calibrator (CRC-15R®, Capintec, 7 Vreeland Road, Florham Park, New Jersey, USA) before being mixed

with the infusion fluid. The activity was measured both over the infusion site and over the thyroid gland at a distance of 30 cm using a gamma detector. All activity measurements with the gamma detector were done with a counting time of 30.0 seconds. The blood samples taken during the study were analyzed by a dedicated gamma counter (2480 Wizard$^{2}$™ Gamma Counter, PerkinElmer, Waltham, Massachusetts, USA). All activity measurements were decay corrected to the start of the infusion.

**Sample size**

The sample size was based on a previous study with healthy older adults.[119] They reported an absorption constant on 2.29 hour$^{-1}$ with a standard deviation of 0.3. We speculated a difference in the absorption constant between the ill and non-ill on 15%. With an alpha of 0.05 and a beta of 0.8, we would need 6 patients. As noted above, the circumstances did not allow the case-control part of the study to be performed, but the sample size was kept.

**Statistical analysis and calculations**

Categorical variables are presented using numbers and percentages, and continuous variables are presented as mean and standard deviation (SD).

For each patient, we calculated a conversion factor for measurement at the infusion site to enable converting measured activity (counts per second, cps) to ml of infused fluid. This patient-specific conversion factor was calculated using the slope of the initial linear part of the activity curve (0-10 minutes). We use the 0-10 minutes value to reduce error from the amount of fluid already absorbed. We calculated the fraction of the infused fluid still present in the subcutaneous space at time *t* after the end of the infusion:

$$\text{volume}_{SC} = \text{measured activity} \times \text{patient-specific conversion factor}$$

$$\text{fraction present in the SC space} = 100\% \times (\text{volume}_{SC} / 235 \text{ ml})$$

We estimated the absorption rate in ml/min specifically for our infusion rate in the 10 minutes following the infusion's completion from the reduction in activity over time at the infusion site:

$$\text{absorption rate} = (\text{volume}_{SC} \text{ at } 70 \text{ min} - \text{volume}_{SC} \text{ at } 60 \text{ min}) / 10 \text{ min}.$$

As the absorption rate in ml/min varies over the study (being dependent on the amount of fluid infused but not yet drained), many studies instead report the absorption constant (k). The theoretical relation between the absorption rate and the absorption constant is:

absorption rate (ml/min) = absorption constant ($min^{-1}$) × present $volume_{SC}$ (ml)

where absorption rates in $hour^{-1}$ can be turned into $min^{-1}$ by dividing by 60, e.g. k = 1.2 $hour^{-1}$ = 0.02 $min^{-1}$. Absorption rate estimates are presented as means with standard error of the mean (SEM).

To validate that the absorption rate measured over SC space really did represent a transfer to the blood stream with availability to body physiology, we also measured uptake into the blood and the thyroid gland. We calculated the mean time to 50% absorbed using regression on log-transformed data, corresponding to expecting an exponential decay. To allow for deviations from a purely exponential form, fitting with a quadratic term was also performed. For thyroid and blood data, a sigmoid curve form (probit function, inverse normal) was used to describe the overall shape. The regression analysis on measurements from the SC space is done from the 60-minute mark and onwards. For data from blood and thyroid, it is done from the start of infusion.

The collected data was stored using REDCap version 7.0.11 hosted at Aalborg University Hospital.[117]
All analyses were done using STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) and Microsoft Excel 365® Microsoft 2020©.

## Results

We recruited six patients, three men and three women, from September to November 2020. The mean age of the patients was 81 years (SD 2.1), the mean CCI score was 1.8 (SD 1.3), and the mean number of prescription drugs before admission was 10 (SD 4.1). Three of the patients had a Tilburg Score over two (judged as frail).[95] All baseline measurements can be found in table 1.

None of the patients experienced any adverse reaction during or after the infusion, and all infusions were completed after 60 minutes. In one patient, the indwelling catheter for collecting blood samples clotted after 40 minutes, and further blood samples could not be drawn.

As expected, the infusion site's activity measurements showed that fluid accumulated in the SC space during the infusion (0-60 minutes) At the end of infusion, the mean volume of fluid still present in the SC space was 111 ml (SD 7.8) of the 235 ml of infused, corresponding to 53 % of the infused fluid having been absorbed. The fraction absorbed after 25, 40, 55, 70, and 85 minutes after the completion of the infusion was 74%, 81%, 85%, 88%, and 90%, respectively (figure 1).

Figure 2, 3 and 4 shows the activities at the infusion site, in blood and uptake in the thyroid, respectively. To present an easily interpretable absorption rate, we calculated absorption rates in ml/minute. These numbers are specific for our setup (235 ml infused over 60 minutes) but provide an example of achievable absorption rates. The mean absorption rate estimated from measurement at the infusion site was 127 ml/h (SEM 18.7).

Exponential regression (regression on the logarithm of the values) without a quadratic term found a mean value of the absorption constant k = 1.12 (SD=0.12) $hour^{-1}$. This corresponds to a half-time $t_{½}$ = 0.693/k = 0.62 hour = 37 minutes (95% CI 34-42 minutes). Including the quadratic term and calculating $t_{½}$ as the time where the original value had dropped to 50% found $t_{½}$ = 31 minutes (95% CI 27-35 minutes, Supplementary figure 1), i.e., shorter but of similar magnitude.
The blood data showed that 50% of the plateau value was reached after 48 minutes (95%CI 43-52 minutes, Supplementary figure 2), and from the data from the thyroid gland is it 58 minutes (95% CI 56-60 minutes, Supplementary figure 3).
Statistical analysis of absorption rate versus serum level of albumin found a statistically significant correlation (p = 0.02), with increasing absorption rate with increasing albumin levels. However, this effect's size cannot be calculated with a meaningful result due to the low number of included patients.

## Discussion

We conducted an explorative study to describe absorption rate and availability in the circulation for fluid given through an SC catheter in frail geriatric patients. To our knowledge, this is the first study to explore this type of hydration in this vulnerable patient group. With an infusion of 235 ml over 60 minutes, we found an average absorption rate from the SC space of 127 ml/hour right after the end of the infusion. The rate, however, will depend on the individual setup, but demonstrates that an absorption rate of 127 ml/hour is achievable in frail geriatric patients. Furthermore, our measurements on blood and thyroid confirms that the infused fluid does enter the blood, rather than just spreading within the SC tissue.

In more general terms, regardless of infusion rate, our data indicates that half of the fluid remaining in the SC space after completion of an infusion will be absorbed after about 31 minutes. This number increase slightly to about 37 minutes if a purely exponential function is assumed, (absorption constant k = 1.12 $hour^{-1}$). Such absorption half-lives are markedly longer than the previous study on healthy adults over 65 years that report a half-life of only 18 minutes.[119]

The k value can be used to give an indication of the volume of fluid in the SC space based on the infusion rate. Assuming a purely exponential function, the volume of fluid accumulating at the infusion site will slowly approach a maximum value of

volume pr. hour divided by k. Standard recommendation on SC fluid infusion describes that 1 liter of fluid can be administered subcutaneously over 8-10 hours.[5,31] Assuming 8 hours, this corresponds to 125 ml/hour. A value of k = 1.12 $hour^{-1}$ thus predicts a maximum volume of 125 ml/hour / 1.12 $hour^{-1}$ = 111 ml being temporarily accumulated in the SC space, regardless of how long this infusion continues. The point here is not the specific number 111 ml, but that the accumulated volume is small enough to corroborate this recommendation as a safe procedure, also for ill, older adults.

With 85% of infused fluid absorbed 55 minutes after the end of infusion, the completeness of absorption is lower than reported in studies on a young population aged 21-35. Here, 95% of infusion fluid was absorbed after 45 minutes after the end of the infusion[118], and in healthy older adults aged over 65, no residual activity was found 60 minutes after the end of infusion. The latter study, however, used hyaluronidase that aided the absorption of SC hydration.[55] Our study found that there was still around 10% of the infused fluid retained in the SC space one and a half-hour after the infusion's completion. Our data did not extend beyond this time point as the procedures wore out our frail patients. All patients requested to be transferred back to the ward at this point.

The important finding of 90% absorbed leaves 10% retained fluid, which is of less clinical relevance when treating the mildly dehydrated patients as SC hydration prescriptions are often made in round numbers.[56]

We found a statistically significant effect of albumin on the absorption rate, with increased albumin levels increasing the absorption rate as expected, but further studies with more participants are required to estimate the size of this effect.

Our study showed that activity measurements over the thyroid gland could be used as a qualitative confirmation that the infused fluid has become part of body physiology, without the need for intravenous cannulation.

**Limitations**

As the radioactive tracer is distributed in the body, the activity measurement will include a background signal from already-distributed activity. However, the detector's collimation ensures that it measures only locally, i.e., a small fraction of the whole body. For this reason, the background signal will be only a tiny fraction of the measured signal and probably not have any effect on our results. Our study infused isotonic saline, and the absorption rate may be different from other types of infusion fluid. The amount of fluid infused is lower than what is typical used in a clinical setting, and the absorption rate and residual fluid in the SC space could be different if 500 ml or 1000 ml were infused over a longer duration. We had planned to have the patients return for a second procedure eight weeks after discharge to investigate the difference between acutely ill and not acutely ill. However, due to time limitation,

restrictions from COVID-19 pandemic, and patient frailty, this was not feasible. However, this paper reports the secondary outcomes listed in our clinicaltrial.gov registration. Finally, our sample was relatively small with just six patients, but results were marked and uniform in all patients, conforming to a reliable absorption portrayal.

In conclusion, we found clinically acceptable absorption rates from the SC space of around 127 ml/ hour right after the end of the infusion in frail geriatric patients with our infusion setup. A small proportion of the infusion fluid was still present in the subcutaneous space one hour after the infusion completion of the infusion. To guide clinicians, our results suggest that one liter of fluid can be administered to the frail geriatric patient over eight hours. Our results are uniform, but the limited sample size encourages further studies to corroborate our results.

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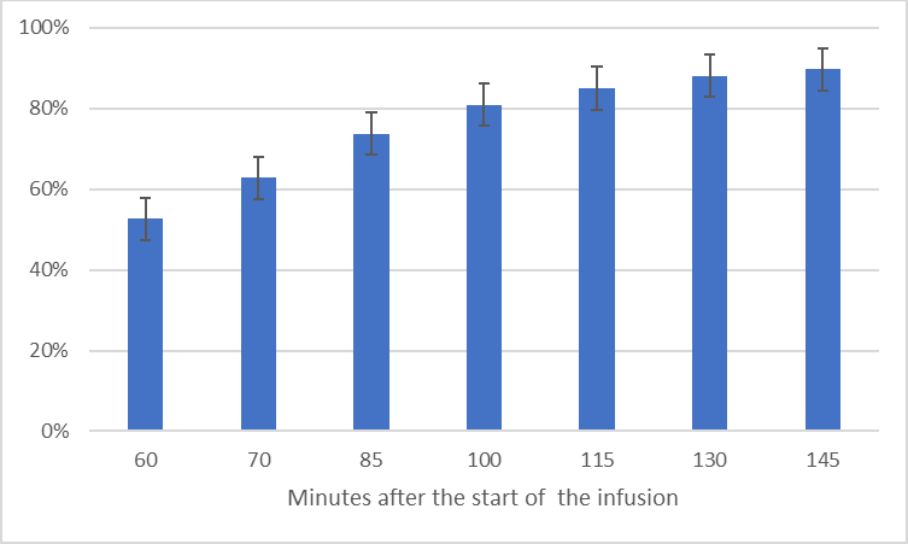
**Acknowledgments**
Statistical assistance by Niels Henrik Bruun, Msc, Unit of Clinical Biostatistics, Aalborg University Hospital, regarding curve fitting is thankfully acknowledged.

## Tables and figures

**Table 1.** Baseline values of the six patients.

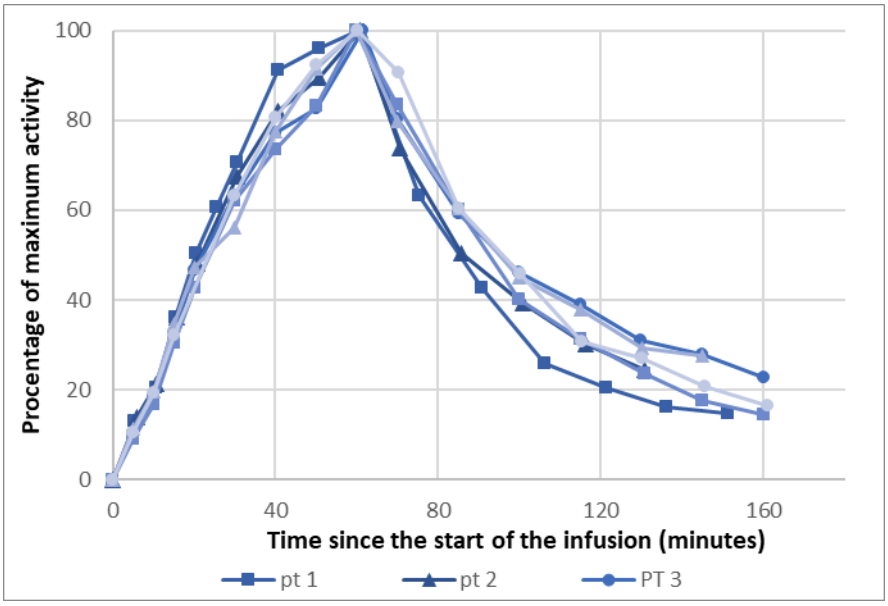
| | **Mean (SD)** |
|---|---|
| **Number of patients** | 6 |
| **Age** | 81 (2.1) |
| **Sex (male/female)** | 3/3 |
| **Number of known comorbidities** | 4.6 (1.2) |
| **Charlson Comorbidity Index**[94] | 1.8 (1.3) |
| **Tilburg frailty scale** [95] | 3.8 (2.4) |
| **Number of prescription drugs** | 10 (4.1) |
| **Treated with anti-coagulant medication** | 1 (16.7%) |
| **Systolic Blood Pressure (mm Hg)** | 122 (9.8) |
| **Diastolic Blood Pressure (mm Hg)** | 71 (5.7) |
| **Pulse (/min)** | 81 (21) |
| **C-reactive protein (mg/l)** | 62 (38) |
| **Hemoglobin (mmol/l)** | 6.2 (0.6) |
| **Sodium (mmol/l)** | 141 (1.6) |
| **Potassium (mmol/l)** | 3.9 (0.2) |
| **Urea (mmol/l)** | 9.3 (2.2) |
| **Creatinine (µmol/l)** | 97 (42) |
| **eGFR (ml/min/1.73m$^2$)** | 62 (24) |
| **Albumin (g/l)** | 28 (4.2) |
| **Osmolality (mmol/kg)** | 297 (5.5) |

**Figure 1.** Mean percentage of fluid absorbed over time across the six patients



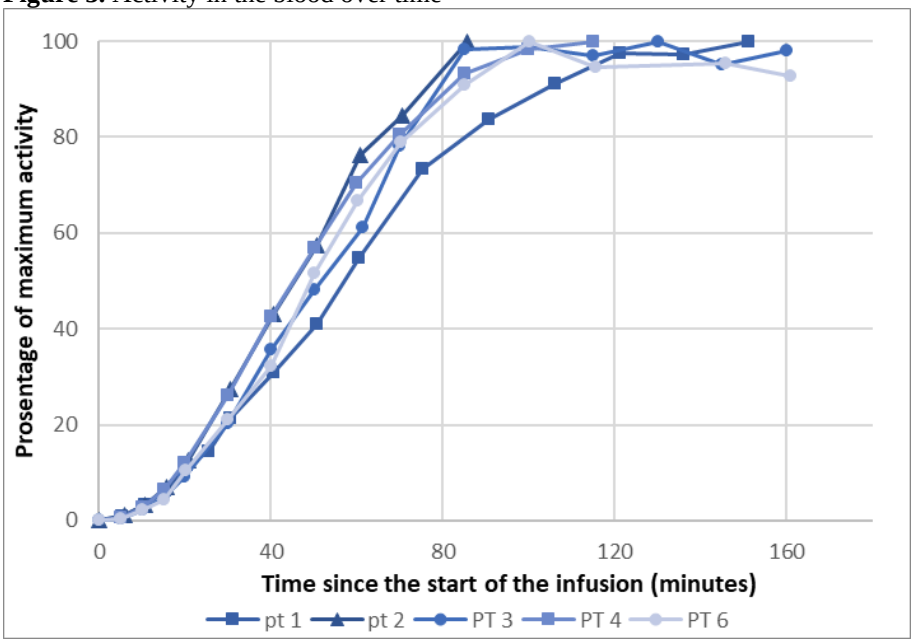

Graphical representation of the mean percentage of infused fluid absorbed over time across all six patients. The X-axis is in minutes after the start of the infusion. The infusion was complete after 60 minutes. The Y-axis is in percent.

**Figure 2**. Activity at the infusion site over time



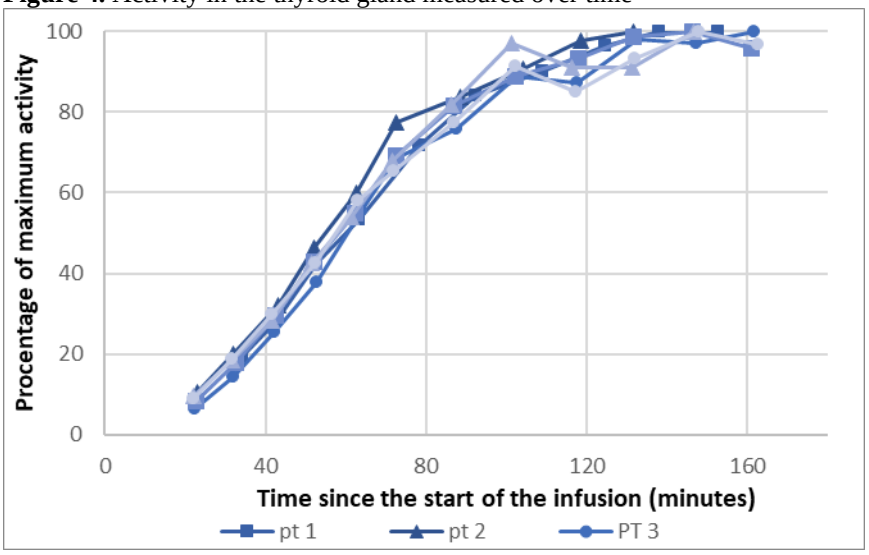

Abbreviation: PT: Patient. Graphical representation of the activity over the infusion site. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity.

**Figure 3.** Activity in the blood over time




Abbreviation: PT: Patient. Graphical representation of the activity in the blood. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity. Data from patient number 5 is missing as the indwelling catheter for the collection of blood samples clotted.

**Figure 4.** Activity in the thyroid gland measured over time

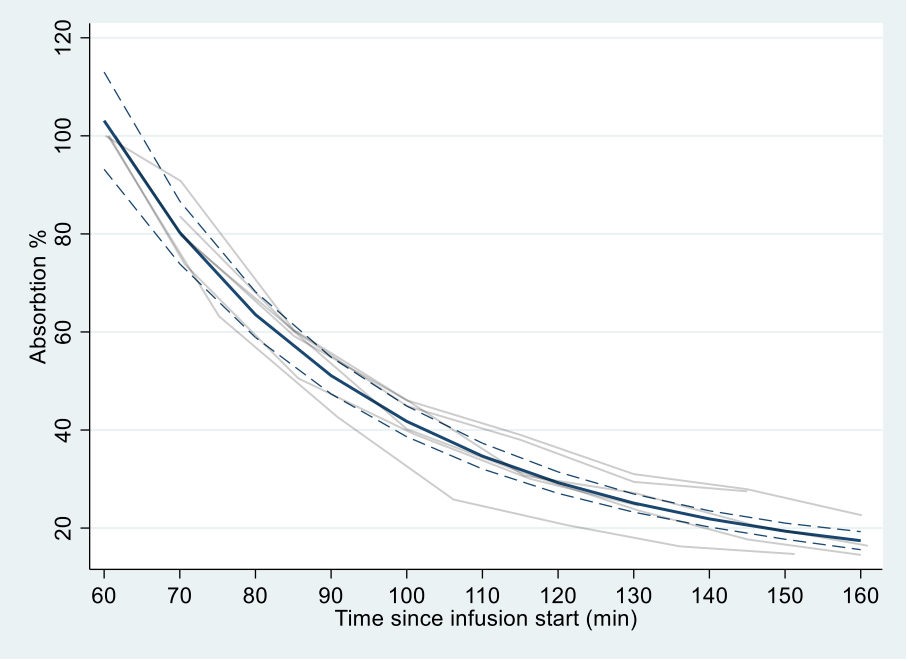



Abbreviation: PT: Patient. Graphical representation of the activity over the thyroid gland. The infusions ended after 60 minutes. All data points are normalized to a percent of the maximum value of a given series. The X-axis is in minutes after the start of the infusion. The Y-axis is in percentage of maximum activity.

**Supplemtary to**

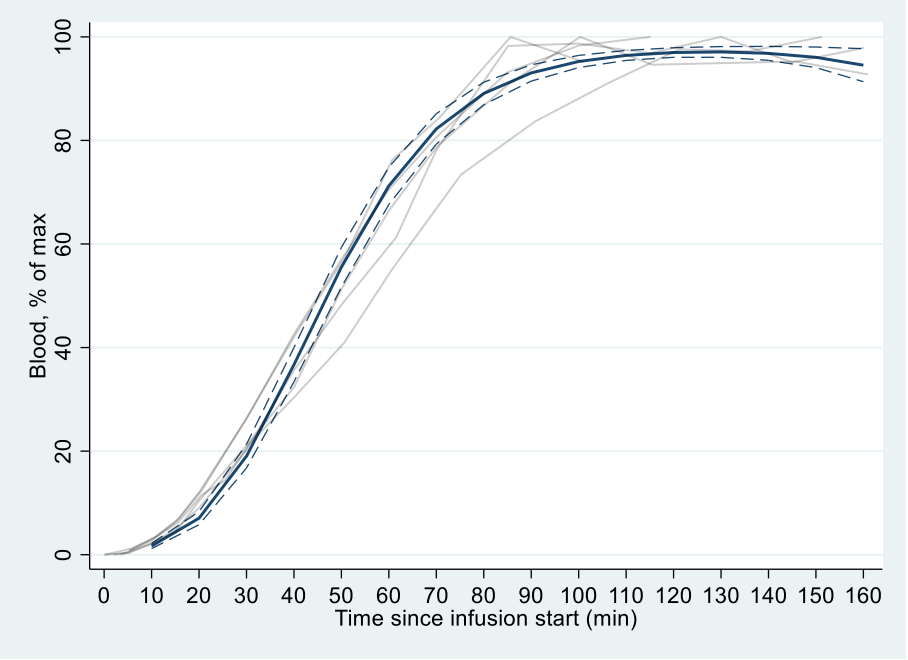
# Absorption Rate of Subcutaneously Infused Fluid in Ill Multimorbid Older Patients

**Supplementary figure 1.** Mixed logistic regression with quadratic effect on fluid remaining in the SC space.



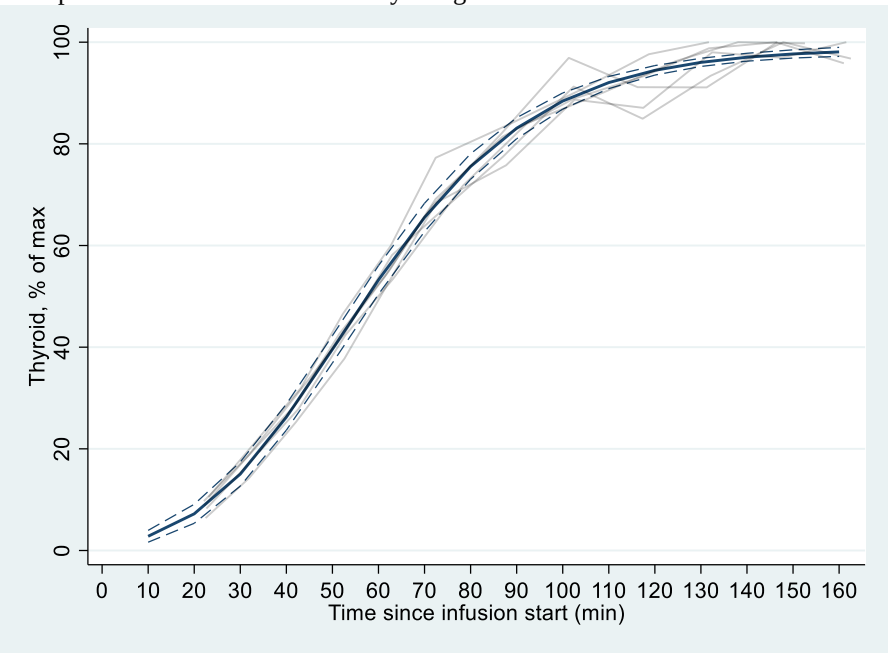

Change in activity at the infusion site after the end of infusion (60 minutes). The y-axis is percentage of maximum activity. The blue line is the fitted curve, the dashed lines are the 95% confidence for the fitted line, and the gray lines are the actual measurements from our patients.

**Supplementary figure 2.** Mixed logistic regression with quadratic effect on absorption based on data from the blood samples.




Change in activity in the blood. The y-axis is percentage of maximum activity. The blue line is the fitted curve, the dashed lines are the 95% confidence for the fitted line, and the gray lines are the actual measurements from our patients.

**Supplementary figure 3.** Mixed logistic regression with quadratic effect on absorption based on data from the thyroid gland.




Change in activity in the thyroid gland. The y-axis is percentage of maximum activity. The blue line is the fitted curve, the dashed lines are the 95% confidence for the fitted line, and the gray lines are the actual measurements from our patients.