Harms and Benefits of Subcutaneous Hydration in Older Patients

Systematic Review and Meta-Analysis

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TITLE

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

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IMPACT STATEMENT

We certify that this work is novel and specifically adds a high-quality and thorough review of all available literature on the harms and benefits of subcutaneous hydration. Furthermore, this review adds valuable information relevant in the clinical care of older persons, and it could potentially insure the most fitting method for parenteral hydration is chosen.

Manuscript word count: 3445, 3 figures and 2 tables

ABSTRACT

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

Data Sources: MEDLINE, EMBASE, CINAHL, CENTRAL, Web of Science and trial registries were searched from inception to 5 November 2019 for any type of study on SC hydration without language restrictions.

Study Selection: Studies of any design were eligible if they used SC hydration in older patients.

Data Extraction: Two reviewers independently extracted the data and assessed the risk of bias of individual outcome**.**

Data Synthesis: Thirty-one publications from 29 studies met the eligibility criteria. Six randomized controlled trials provided data for the meta-analyses. The subgroup analysis including only studies with the lowest risk of bias showed fewer adverse effects associated with SC compared with intravenous (IV) (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, high-quality studies showed an incidence rate of 90 adverse effects per 1000 infusions with SC hydration and 130 (95% CI 102-169) adverse effects per 1000 infusions with IV hydration. The confidence in this estimate is moderate. Secondary outcomes showed that SC hydration is less efficient compared to IV as estimated by the surrogate markers of reductions in s-osmolality and volume of fluid infused; however, markedly reduces the risk of agitation (RR 0.42, 95% CI 0.22-0.79, p=0.007, I^2=65%, n=3), and is 3.2 minutes faster to setup. Nonetheless, the quality of evidence of all secondary outcomes is low or very low.

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

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

INTRODUCTION

Dehydration is a common and potentially dangerous condition in older patients.[1] 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.[2] The infusion of fluid is required when oral rehydration is insufficient. Intravenous (IV) hydration is the common choice because large volumes 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.[3] This often forgotten method has been reported in recent decades as an easy and safe method for parenteral hydration of geriatric patients with mild to moderate dehydration.[4–6] Despite these studies, SC is still reported to be underused.[7–9]

Fluid infused subcutaneously reaches the circulation within an hour, according to the results of a radioisotope study[3]. Hence, the hydration effect should be similar between SC- and IV-infused fluid, although a small delay may occur with SC infusion. A clinically relevant difference between IV and SC hydration might be in the risk of adverse effects. Furthermore, from our clinical 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 had important methodological shortcomings. They did not include a transparent and comprehensive systematic search of the literature, *a priori* registration or adequate evaluation of risk of bias.[4–6] These limitations led us to conduct a systematic review and meta-analysis following the PRISMA guidelines.[10] The primary aim was to compare the risk of adverse effects using SC vs IV hydration in older

patients and to estimate the incidence and profile of adverse effects. Additional aims were to compare the clinical effect of SC hydration vs IV. Thus, the overall aim was to asses if 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)[10] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to rate the quality of evidence and present the results.[11] The study was *a priori* registered in PROSPERO (CRD42017071912)

Eligibility criteria

To achieve a comprehensive overview and following the recommendations of the Cochrane Handbook[12] on reviews of adverse effects, we included relevant studies of all designs (randomized controlled trials (RCTs), observational studies and case reports) and types (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 restricted inclusion 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 no comparator in observational studies. Studies on the SC infusion of drugs, parenteral nutrition, the relevance of hyaluronidase or those 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 type of 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 the date of the final search, 5 November 2019. Authors of unpublished and ongoing trials were asked if data were available to be included in this review. The full search string for the included databases can be found in Supplementary Text S1.

Study selection

Two reviewers (MBD and SA) independently assessed eligibility, initially by title and abstract and subsequently by full text. We settled disagreements by consensus or by involving a coauthor (MGJ).

Data items and collection process

We first translated all non-English publications using a translate engine[13], and when insufficient a translator provided a written translation. Two reviewers (MDB and SA) independently extracted the data using piloted forms. The following data were extracted: study and patient characteristics, type of fluid infused, the use of hyaluronidase and the duration of treatment. In all studies with missing data, we attempted to contact authors by

e-mail to obtain this pertinent information. To estimate exposure, we extracted the total number of infusions. If 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".[12] Additionally, we divided adverse effects into serious and minor and adhered to the WHO definition of serious adverse effects as any consequence of infusion requiring treatment.[14] All outcome data is extracted as intention to treat.

Risk of bias in individual studies

We used the Cochrane Risk of Bias 2.0 (RoB 2.0) to assess the risk of bias in RCTs[15]; furthermore, we assessed the risk of bias in observational studies based on the key criteria listed by GRADE[16]. 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 outcomes measures. We did not combine RCTs and observational studies in the meta-analyses. For the meta-analysis, we applied an inverse variance random-effects model (DerSimonian-Laird[17]). Statistical heterogeneity was explored using the I^2 statistic. We report dichotomous outcomes in risk ratio (RR) and continuous outcomes in mean difference (MD).

When the same outcome was reported using different scales, we used the standardized mean difference (SMD). Stata version 15 (StataCorp LLC TX College Station. 2017) and ADMETAN[18] was used to perform the analyses. Comparisons were 2-tailed with a 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 by the number of infusions.

As recommended by Cochrane RoB 2 meta-analyses were stratified by the overall risk of bias.[15] Prespecified subgroup analyses of the primary outcome with regard to the addition of hyaluronidase and the setting of the studies was also conducted. Furthermore, we performed a separate meta-analysis on major and minor adverse effects as an explanatory analysis.

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 and calculated an overall incidence rate. In addition, we estimated the incidence by combining data from studies at the lowest risk of bias only. We used this incidence and the RR from our lowest risk of bias subgroup to calculate the absolute risk difference according to the GRADE guidelines[19].

Additional analyses

As dehydration cannot be defined by a single symptom, sign or laboratory value[2,20] we conducted meta-analyses of all available surrogate markers of dehydration and clinical effect of hydration treatment if they were reported by at least two RCTs. Furthermore, we compared time spent on catheter insertion.

RESULTS

Study selection

A total of 5064 references were screened by title and abstract, of which 242 qualified for full-text screening (figure 1. PRISMA flow chart[21]). Most publications excluded during full-text screening were reviews or descriptions of subcutaneous hydration. In addition, 9 publications were cross-sectional studies and 4 were case reports with no information on adverse effects. Furthermore, we found two relevant study protocols, of which one had no data yet[22] and the author of the other e-mailed us a poster but had no full-text report. The poster had insufficient data to be included in the meta-analysis [23]. The individual reasons for exclusion of publications read in full-text form can be found in Supplementary Text S2.

Study characteristics

Thirty-one publications representing 29 different studies met our eligibility criteria. The designs of the included publications were: 7 RCTs[24–30], 1 case-control study[31], 11 prospective cross-sectional studies[32,33,42,34–41], 6 retrospective cross-sectional studies[43–50] and 4 case reports[51–54]. Fourteen studies were performed in a hospital setting, 6 in short-/long-term care facilities and nine included a combination of hospital and short-/long-term care or home-based treatment, while 1 did not report the setting. The median age 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. 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.

185 Information on which studies replied and what information was delivered is available in
186 Supplementary Text S3.

187 Table 1 provides a summary of the study characteristics of included RCTs and Supplementary
188 Table S1. provides a summary of the outcomes available for extraction. Extracted study
189 characteristics for all included studies can be found in Supplementary Text S3. One RCT, four
190 prospective studies and one retrospective cross-sectional study did not report data
191 sufficiently to allow an estimate of the number of infusions or they did not report the number
192 of adverse effects. We attempted to contact the authors to obtain these data, but none
193 responded. Hence, these studies were not included in the data synthesis.

194

195 Risk of bias within studies

196 For the outcome of adverse effects, four out of six RCTs had an Overall RoB 2 of *Some*
197 *Concern*[24,28–30] and the remaining two had a *High risk of bias*[25,26]. Across all outcomes, no
198 studies reported an *a priori* protocol or statistical analysis plan. In addition, description and
199 measuring of outcomes were often lacking. The RoB 2 of individual RCTs on all outcomes with
200 response to signaling questions can be found in Supplementary Text S4. A table of risk of bias
201 in the observational studies can be found in Supplementary Table S2.

Synthesis of results

Adverse effects

Combining data from the six RCTs[24–26,28–30] in a meta-analysis, the studies with the lowest overall risk of bias (*Some concern*) showed a statistical significant 31% lower risk of adverse effects with SC hydration compared with IV (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). One RCT did not report the number of adverse effects observed and was therefore omitted from the meta-analysis; however, the authors did report no difference in observed complications.[27] A subgroup meta-analysis on the setting and use of hyaluronidase can be found in Supplementary Figures S1 and S2.

To estimate the incidence rate of adverse effects, we combined all included studies with suitable data (five RCTs and fourteen observational studies)[24,25,37,39,40,42,44–49,26,50,28–31,33–35]. The data showed an incidence rate of 53 adverse effects per 1000 infusions (95% CI 48 to 57, n=19, 10,970 infusions) for SC hydration. Combining only studies with the lowest risk of bias (four RCTs and four observational studies)[24,28–31,33,37,39] an incidence rate of 90 adverse effects per 1000 SC infusions (95% CI 80 to 101, n=8, 2876 infusions) was found. In absolute numbers, patients experienced 130 adverse effects with IV hydration per 1000 infusions (95% CI 102 to 169, table 2). This absolute number is based on a calculation mentioned in the methods section under data synthesis and analysis.

Serious adverse effects of SC from all studies and the lowest risk of bias studies showed incidence rates of 2.2 adverse effects (95% CI 1.3 to 3.1, n=19, 10,970 infusions) and 3.7 adverse effects per 1000 SC infusions (95% CI 1.5 to 5.9, n=8, 2876 infusions), respectively. Incidences of the different minor adverse effects (the lowest risk of bias studies only) can be

seen in Figure 3. Furthermore, meta-analyses on serious adverse effects and the different types of adverse effects can be found in Supplementary Figures S3 and S4 respectively.

The included case reports describe 1 case with caecal perforation from SC hydration in a lean 86-year-old female[51] and 1 case with erythema progressing to necrosis from SC hydration[52]. The remaining case reports describe common adverse effects reported in other publications.

Clinical effects of the hydration treatment

The included studies used an array of surrogate markers of dehydration in an attempt to evaluate how well the SC and IV hydration treated the problem. However, most of these markers were reported in a non-uniform manner making them unfit to include in a meta-analysis. Only s-osmolality was reported sufficient homogeneously to be combined in a meta-analysis, and this analysis showed IV hydration lowering serum osmolality statistical significantly more than SC hydration (MD 5.75 mmol/kg in favor of IV, 95% CI 0.13 to 11.4, p=0.045, I^2=0.0%, n=2, Table 2 and Supplementary Figure S5)[24,30]. The other surrogate markers of dehydration examined by different studies were creatinine levels[28–30], urea levels[28,30], patient discomfort[29] and Barthel Score[29]. Worth noting is that none of the studies reported a statistically significant difference between the two groups in any of the variables.

We examined the effects of the hydration treatment by the surrogate markers of death, the volume of fluid infused and agitation as these variables were reported by more than one study. Three studies reported deaths[24,28,30] and three did not[26,29,55]. No difference between SC and IV was found (RR 1.26 in favor of IV, 95% CI 0.25 to 6.34, p=0.78, I^2=0.0%, n=3, Table 2 and Supplementary Figure S6)[24,28,30]. Three studies reported volume of fluid infused[28–30] and

246 the meta-analysis showed a statically significant difference in favor of IV hydration between
247 the groups (SMD 0.62, 95% CI 0.24 to 1.01, p=0.0027, I^2=50%, n=3, Table 2 and Supplementary
248 Figure S7)[28–30]. Three studies reported agitation as an outcome[26,28,30]. There was a statistically
249 significant difference in favor of SC hydration in the risk of agitation between the groups (RR
250 0.42 in favor of SC, 95% CI 0.24 to 0.78, p=0.007, I^2=65%, n=3, Table 2 and Supplementary
251 Figure S8)[26,28,30]. It should be noted, however, that the included studies in this analysis all
252 included patients with cognitive impairment.

253 Data from 2 studies[26,29] showed a statistically significant difference in catheters insertion time
254 between SC and IV (mean difference 3.2 minutes faster to insert SC, 95% CI 1.5 min. faster to
255 4.9 min. faster, p<0.001, I^2=46.2%, n=2, Table 2 and Supplementary Figure S9)[26,29]. The
256 reported mean time spent on IV catheter insertion was 5.2 minutes[26,29].

257 ## Risk of bias across studies

258 Evaluating the risk of publication bias, we identified one unpublished RCT comparing IV with
259 SC. A poster from this study describes fewer complications with SC hydration than with IV.
260 Based on a funnel plot, there is no suspicion of publication bias, but cautious interpretation
261 is important with only 6 studies (Supplementary Figure S10).

262 We found no overall risk of selective reporting bias on adverse effects, as we found no RCT
263 on SC hydration vs IV without this outcome. However, there is a potential risk of altering the
264 definition of adverse effects following data collection, as none of the included studies had an
265 a priori registration. This also accounts for markers of hydration status.

266

DISCUSSION

Summary of evidence

Most older patients require fluid therapy due to an increased risk of dehydration.[56] Hydration treatment is a cornerstone in the treatment of older patients, but gaining IV access can be time-consuming in multimorbid patients.[57] Subcutaneous hydration is an alternative method and the data presented in this study show that SC hydration is a safer alternative than IV hydration. In absolute numbers, based on data from the studies with the lowest risk of bias, patients receiving SC hydration experienced 90 adverse effects per 1000 infusions vs. IV hydration with 130 adverse effects per 1000 infusions. The level of heterogeneity was very low, which increases the confidence in the estimate. However, none of the studies had a low risk of bias and in the four studies that contributed to the estimate all had an overall RoB2 of *Some Concern*.[24–26,28,30] This contributes to a reduction in the credibility of the estimate, and our overall confidence in the estimate is moderate (Table 2). Therefore, the results provide a good indication of the likely estimate.

Both IV and SC infusions are associated with a low incidence rate (~ 10%) of adverse effects. The majority of these are minor adverse effects causing mild discomfort to the patient and requiring reinsertion of the needle. Only 1 in 270 infusions for both IV and SC will lead to a major adverse effect that will increase the duration of hospital stay or require additional treatment. However, care should be taken when the SC needle is inserted into the abdomen, as there is a risk of perforation of the large intestines when treating very thin or cachectic patients. Furthermore, the main component helping absorb fluid from subcutaneous space

into the blood is albumin.[58] 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 on the volume of fluid that can be infused. Guidelines describe a maximum of 1.5 L of fluid per needle per day.[2,6] The listed indication for SC hydration is treatment of mild to moderate dehydration or fluid supplementation in patients with reduced oral intake at risk of dehydration.[2] These indications are supported by our finding of a lower volume of fluid infused with SC compared to the IV route and the reduced lowering of serum osmolarity. Overall, the quality of evidence regarding the effect of hydration treatment comparing the two methods is very low, making it very likely that the true effect is substantially different (Table 2). There were very few deaths reported and the meta-analysis failed to provide any meaningful estimate due to a very large confidence interval. Finally, the 58% lower risk of agitation with SC hydration is potentially very interesting as this condition is associated with increased morbidity and mortality.[59] However, the studies included in this meta-analysis all had some concern of risk of bias and the outcome was reported as agitation and not delirium. The confidence in this estimate is low, and the likelihood that the true estimate will be substantially different is high (Table 2). Giving the importance of this outcome further research is much needed to investigate this.

With a mean time spent on IV catheter insertion of 5.2 minutes, the 3.2 fewer minutes required to insert the SC catheter may be relevant to the limited staff resources in modern healthcare. Nevertheless, this result should be interpreted with caution because most data were obtained from a single study with a high risk of bias combined with a high level of

statistical heterogeneity. The confidence in this estimate is very low, and the likelihood that the true estimate will be substantially different is high (Table 2).

The strengths of the current review include (1) a comprehensive search; (2) inclusions of all study designs and reports regardless of publication languages; (3) high methodological quality; and (4) all outcomes reported in absolute numbers to support clinical interpretation.

Limitations

Review level

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

Outcome level

A major limitation of the results in this review is the limited number of RCTs. Furthermore, most of our analyses were conducted with data from studies with at least Some Concern of bias. The incidence of adverse effects would likely be higher than what is reported if all studies adhered to the full list of events. Finally, we were only able to retrieve additional data from a few of the studies.

In conclusion, there is acceptable evidence that SC hydration is a safer alternative method of parenteral hydration compared to IV. The recommendations that only mild to moderately dehydrated patients should be treated with SC hydration is reasonable based on the results on the effectiveness presented here; however, the quality of the evidence is very low. Finally, the reduced risk of agitation found in patients with cognitive impairment when treated with

330 SC hydration is intriguing. Overall, more high quality studies are needed to establish the true

331 benefits and harms of SC hydration.

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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

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Supporting information

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

Figure legend

Figure 1. PRISMA flowchart

Figure 2. Meta-analysis on 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 pooling of Risk Ratios using the random-effects inverse-variance model with DerSimonian-Laird estimate of tau^2.
The dashed line represents the overall pooled estimate.

Figure 3. Incidence of minor adverse effects per 1000 infusions

Footnote: Data from the lowest risk of bias studies (in total n = 7, with 2171 infusions)[24,28–30,33,37,39]. I-bars represent 95% confidence interval. One study reported data on serious and total number of minor adverse effects but not on specific minor adverse effects[31]. This is the

reason for the discrepancy between the number of included studies and infusions in figure 3 and the reported incidence of 90 per 1000 infusions.

Table 1 Characteristics of 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[25] 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[24] 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[28] 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[29] 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[27] China English	**57** (Unable to calculate number of infusions)	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[30] 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[26] Turkey English	**30** Cross-over 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 dehydrated 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 infusion. No data on how long many days this took.

Abbreviations: RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, G: Gauge.

[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.

Table 2. GRADE Summary of findings: subcutaneous hydration

No of studies (design)	n/N of infusions SC	n/N of infusions IV	Relative effect measure (95% CI)	Absolute effect	Quality of the evidence
Risk of adverse effects					
Lowest risk of bias subgroup (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 serum osmolality"					
(2 RCTs)	51[f]	50[f]	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[b,c,d]
Effect of hydration treatment, "Death"					
(3 RCTs)	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[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 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.[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 will 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 (1.48: 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[b,e]

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

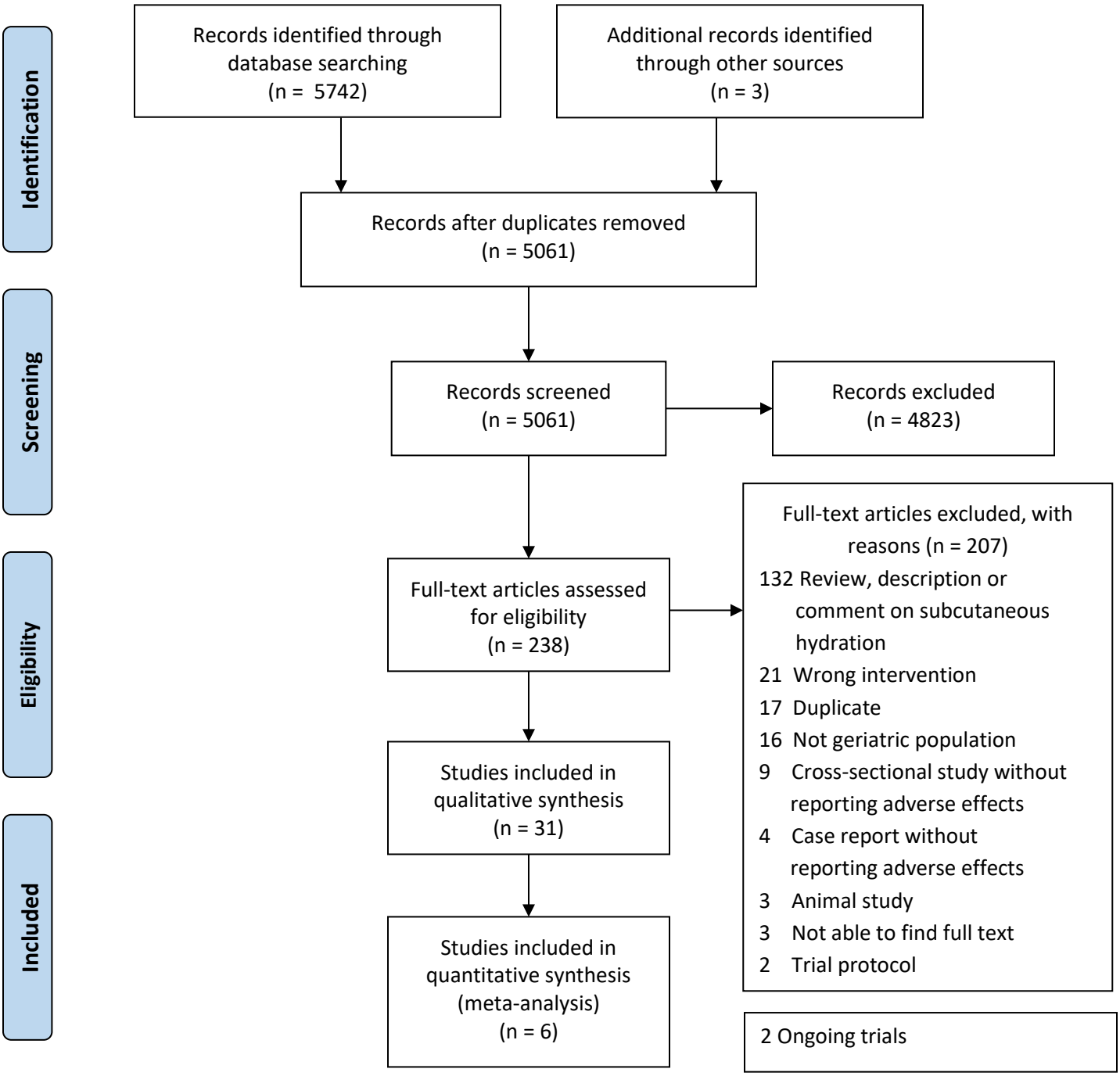
GRADE Evidence profile table can be found in Supplementary Table S3

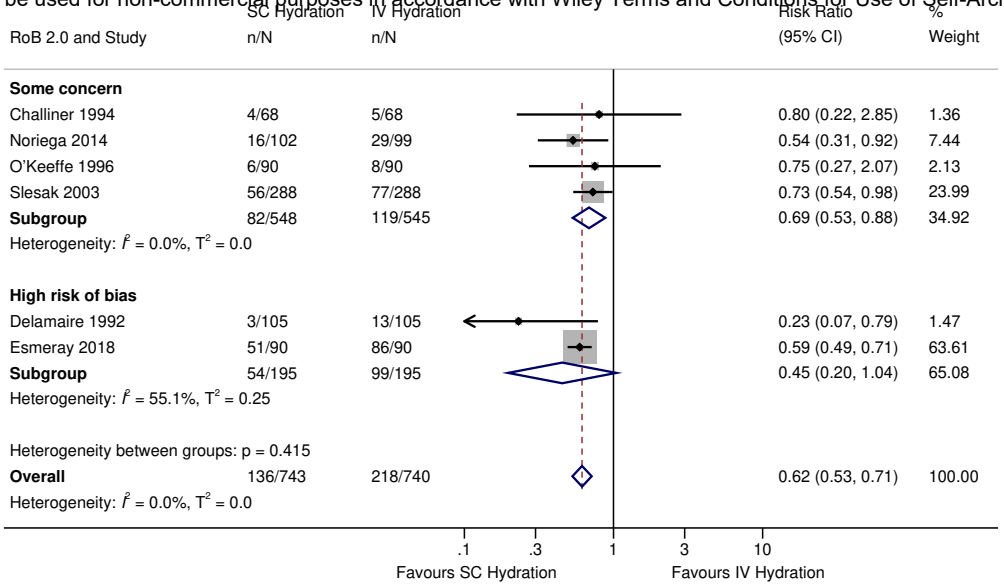
[f] Number of patients evaluated for this outcome

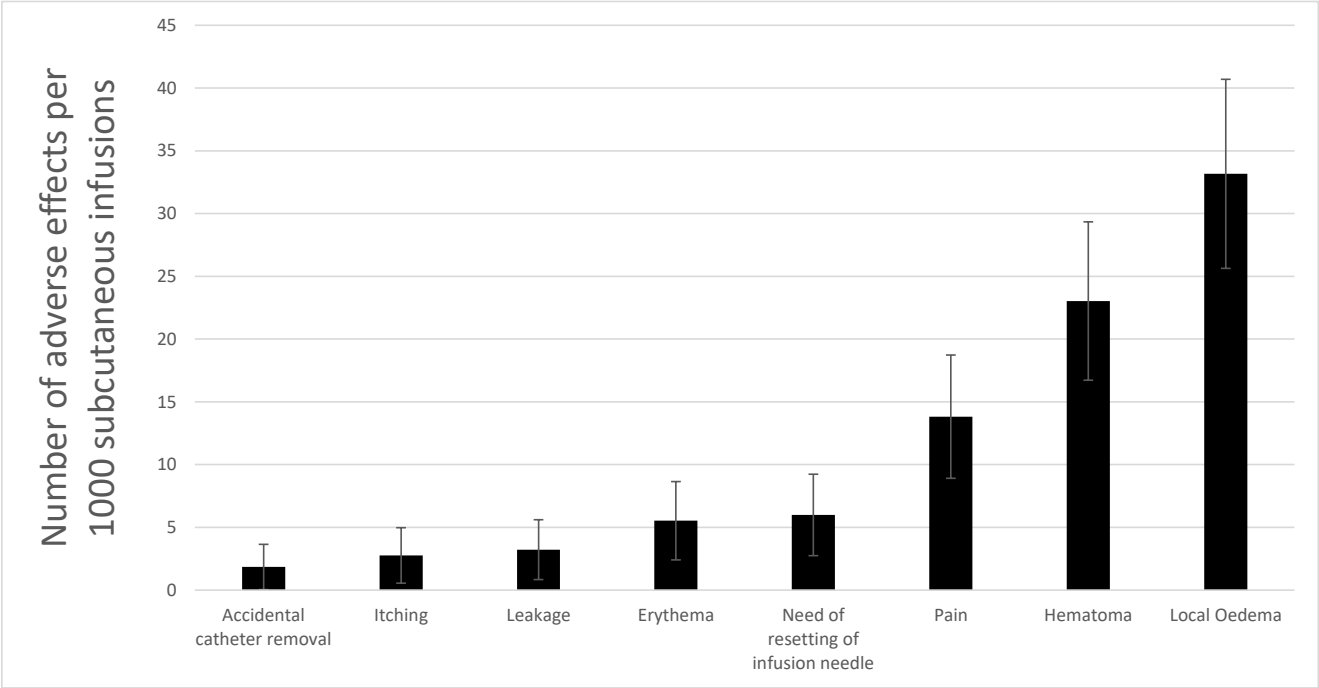
[g] We have use standard mean difference (SMD) as included studies reported either volume per day or volume overall.

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

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







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 Text S2. Exclusions reason for papers read in full text

Listed alphabetical by title of paper.

1. Gabriel J. A guide to Subcutaneous Infusion. British Journal of Nursing 2019;28(sup14c):1-7 2019 *Exclusion reason:* Review, description or comment on subcutaneous hydration;
2. Candon HL, Amirov C, Toen J V. A multifaceted intervention to address a case cluster of cellulitis associated with hypodermoclysis in a geriatric complex continuing care unit. Can J Infect Control. 2010;25(2 PG-101-106):101-106. *Exclusion reason:* Wrong intervention;
3. M. V, D. H, J.L. W, G.B. C, J. A. A prospective study: Hypodermoclysis performed by caregivers in the home setting. J Clin Oncol. 2014;32(31 SUPPL. 1):no pagination. *Exclusion reason:* Duplicate;
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5. Bruera E, Neumann CM, Pituskin E, Calder K, Hanson J. A randomized controlled trial of local injections of hyaluronidase versus placebo in cancer patients receiving subcutaneous hydration. Annals of oncology. 1999;10(10):1255-1258 *Exclusion reason:* Wrong intervention;
6. E. B, K.O. A, J.L. P, et al. A randomized, controlled trial of parenteral hydration in patients with advanced cancer. J Clin Oncol. 2010;28(15 SUPPL. 1):no pagination. *Exclusion reason:* Wrong intervention
7. Cohen JS. A summary of complications of fluid therapy. Vet Clin North Am. 1982;12(3):545-558. *Exclusion reason:* Animal study
8. POLACEK E, JECH C. Absorption of 0.9 o/o sodium chloride injected subcutaneously in dehydration shock. Cesk Pediatr. 1956;11(6 PG-406-411):406-411. *Exclusion reason:* Animal study;
9. ABBOTT WE, KRIEGER H, BABB LI, SAVOIE E, LEVEY S. Administration of dextran by hypodermoclysis. Surg Gynecol Obstet. 1954;99(2 PG-147-150):147-150. *Exclusion reason: I*ndication not hydration;
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15. Cline M, Gershon K. An alternative to IV fluids - Hypodermoclysis. Oncol Nurs Forum. 2005;32(2 PG-450-450):450. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
16. Burgoyne G. Appropriate use of hypodermoclysis. Can Fam Physician. 1993;39(Journal Article PG-24, 26):24,26. *Exclusion reason:* No patients data;
17. Bear AJ, Bukowy EA, Patel JJ. Artificial Hydration at the End of Life. Nutr Clin Pract. 2017;32(5 PG-628-632):628-632. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
18. Boland E, Johnson M, Boland J. Artificial hydration in the terminally ill patient. Br J Hosp Med. 2013;74(7 PG-397-401):397-401. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
19. Smith L, Amelia EJ, Mueller M. Artificial Nutrition and Hydration at End of Life. Home Healthc Now. 2015;33(1 PG-38-43):38-43. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
20. Ying I. Artificial nutrition and hydration in advanced dementia. Can Fam Physician. 2015;61(3 PG-245-8, e125):245-248, e125. *Exclusion reason:* Review, description or comment on subcutaneous hydration;

21. Thomas JR, Yocum RC, Haller MF, von Gunten CF. Assessing the role of human recombinant hyaluronidase in gravity-driven subcutaneous hydration: the INFUSE-LR study. J Palliat Med. 2007;10(6 PG-1312-1320):1312-1320. *Exclusion reason:* Not geriatric population;
22. Tine S., Phung-Nguyen A.-T., Abdoo Wahed Y., Martel C., Ratiney R., Perilliat I. Évaluation de la pertinence des perfusions sous-cutanées en unité de soins de longue durée. Pharm Hosp. 2009;44(177):70-74. *Exclusion reason:* Cross-sectional study without adverse effects
23. Soremekun OA, Shear ML, Connolly J, Stewart CE, Thomas SH. Basic-level emergency medical technician administration of fluids and glucose via enzyme-assisted subcutaneous infusion access. Prehosp Disaster Med. 2012;27(3 PG-220-225):220-225. *Exclusion reason:* Not geriatric population;
24. BERMAN JK, PIERCE GS, BEST MM. Burn shock; its treatment with continuous hypodermoclysis of isotonic solution of sodium chloride into the burned areas; clinical studies in 2 cases. Arch Surg. 1946;53(5):577-587. *Exclusion reason:* Not geriatric population
25. Finn M. Canadian perspective. Hypodermoclysis: an old solution revisited. J Gynecol Oncol Nurs. 1996;6(3 PG-32-33):32-33. *Exclusion reason:* Not able to find full text;
26. de la RE, Zamora Monge G. Canalization of a subcutaneous route as a valid alternative for geriatric patients in hospital stay with moderate dehydration. Agora Enferm. 2015;19(1 PG-5-8):5-8. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
27. A.K. D, P. Y, A.K. A, B.B. R. Clinical approach to altered serum sodium levels. Journal, Indian Acad Clin Med. 2006;7(2 PG-91-103):91-103. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
28. LINDSEY D. Clinical Contribution of Hypodermoclysis. Can Fam Physician. 1992;38(Journal Article PG-2801-2801):2801. *Exclusion reason:* Duplicate;
29. Clinical management. J Intraven Nurs. 1998;21(1S):S26-68. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
30. Smith LS. CLINICAL QUERIES. Hypodermoclysis with older adults. Nursing (Lond). 2014;44(12 PG-66-66):66. *Exclusion reason:* Duplicate;
31. Cerchietti L, Navigante A, Sauri A, Palazzo F. Clinical trial. Hypodermoclysis for control of dehydration in terminal-stage cancer. Int J Palliat Nurs. 2000;6(8 PG-370-374):370-374. *Exclusion reason:* Duplicate;
32. C.D. B, J.A. B. Comfort care for patients dying in the hospital. N Engl J Med. 2015;373(26 PG-2549-2561):2549-2561. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
33. Barbosa G, Laís Samara M, Oliceira S, Barbosa J. Complicações da via subcutânea na infusão de medicamentos e soluções em cuidados paliativos. Rev Rene 2019;20(1):1-9 2019 *Exclusion reason:Wrong intervention.*
34. Hall B. Complications of hypodermoclysis (re-emphasis with a case presentation). J Ky Med Assoc. 1968;66(7):626-627. *Exclusion reason:* Not geriatric population;
35. Kala M. Complications of the subcutaneous administration of fluids and possibilities of their solutiones. Interni Med pro Praxi. 2013;15(1):36-37. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
36. Menahem S, Shvartzman P. Continuous subcutaneous delivery of medications for home care palliative patients-using an infusion set or a pump? Support Care Cancer. 2010;18(9 PG-1165-1170):1165-1170. *Exclusion reason:* Wrong intervention;
37. Smulders YM. Continuous subcutaneous infusion in palliative care, an undervalued method. Ned Tijdschr Geneeskd. 2003;147(7 PG-319; author reply 319):319; author reply 319. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
38. Ansari SA, Rivera E, Modawal A. Correction of sodium electrolyte abnormalities with hypodermoclysis in the long-term care setting. J Am Geriatr Soc. 2004;52(4 PG-21-22):S21-S22. *Exclusion reason:* Case report without advese effects;
39. DANGERS of hypodermoclysis. Nutr Rev. 1953;11(8):232-234. *Exclusion reason:* Review, description or comment on subcutaneous hydration
40. Pierrat D. Deep subcutaneous perfusion: a little-known method for rehydrating the elderly. Servir. 1990;38(6 PG-308-309):308-309. *Exclusion reason:* Review, description or comment on subcutaneous hydration;

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176. N.I. C. Taking care of the terminally ill cancer patient: Management of gastrointestinal symptoms in patients with advanced cancer. Ann Oncol. 2004;15(Web Page PG-). *Exclusion reason:* Review, description or comment on subcutaneous hydration;
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195. Bausewein C. Under what conditions is subcutaneous administration of fluid indicated. Internist (Berl). 2007;48(4 PG-439-441):439-441. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
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202. Using subcutaneous fluids in end-of-life care. Nurs Times. 2014;110(40):12-14. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
203. Barton A, Fuller R, Dudley N. Using subcutaneous fluids to rehydrate older people: current practices and future challenges. QJM. 2004;97(11):765-768. *Exclusion reason:* Review, description or comment on subcutaneous hydration;
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been the burdens and benefits to your clients for whom it was used? J Gerontol Nurs. 2000;26(5 PG-48-50):48-50. *Exclusion reason:* Duplicate;

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Table 1 Characteristics of included RCT studies (a landscape copy of Table 1)

Study & year Country Language	Study design	Sample size	Setting	Patient population characteristics	Intervention details	Comparator details	Duration of intervention /comparator	Numbers of infusions	Funding sources of trials
Delamaire 1992 [25] France French	RCT – Open label*	30	No description of setting	Geriatric patients Described as elderly patients. No information on participants hydration status. Mean age: 83 years No information on sex	SC infusion. (no further description)	IV infusion. (no further description)	Mean: 7 days, SD: No data	105 in each group† (7 infusions per participant¶)	No data
Challiner 1994 [24] United Kingdom English	RCT – Open label*	34	Hospital, Elderly Care Unit	Geriatric patients with acute stroke. Dehydrated (mean s-osmolality 296 mOsm/kg baseline) Mean age 83.5 years Male: 23, Female: 11	SC infusion. Two liters of fluid per 24 hours delivered through a 19 G butterfly	IV infusion. Two liters of fluid per 24 hours delivered through an IV access (no further information)	48 hours (predetermined)	68 in each group‡ (4 infusions per participant¶)	No data
O'Keeffe 1996 [28] United Kingdom English	RCT – Open Label*	60	Hospital, acute geriatric unit.	Geriatric patient 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	SC infusion. Up to 2 liters of fluid per 24 hours. 21 G butterfly needle in infraclavicular, scapular, abdominal or thigh areas	IV infusion. Up to two liters of fluid per 24 hours. 18-20 G cannula in forearm veins	48 hours (predetermined)	90 in each group§ (3 infusions per participant¶)	No data
Slesak 2003 [29] Germany English	RCT – Open label	96	Hospital, geriatric wards in the Geriatric Department	Geriatric patients with signs of mild to moderate dehydration (median s-creatinine 1.0 mg/dl; 88) Mean age 85.3 years Male: 29, Female: 67	SC infusion. Up to 1.5 liters of fluid per 24 hours. Butterfly needle 21 G, in SC tissue of thigh, abdomen, or thorax.	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	288 in each group† (6 infusions per participant¶)	No external funding
Luk 2008 [27] China English	RCT – Open label	57	Hospital	Geriatric patient 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	SC infusion. Up to 1.5 liters of fluid per 24 hours. 22 G butterfly needle in the sc tissue of the lateral abdomen.	IV infusion. Up to 1.5 liters of fluid per 24 hours. 18-22 G angiocaths.	Up to 3 days (Predetermined)	Unable to calculate.	Tung Wah Group Hospitals Research Fund
Noriega 2014 [30] Spain Spanish	RCT – Open label*	70	Hospital, Acute Geriatrics unit	Geriatric patients, dehydrated (mean s-osmolality 327 mOsm/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	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.	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)	102 in SC group, 99 in IV group† (3 infusions per participant¶)	No external funding
Esmeray 2018 [26] Turkey English	RCT cross-over – open label*	30	Long-term care. "Private long-stay geriatric care unit"	Geriatric patients with dementia. 60% were dependent for support for fluid intake. Mild/ moderate dehydrated or risk of dehydration. No further information on participants hydration status. Mean age: 82 years Male: 3, Female: 27	SC infusion. 21–23 G butterfly needle	IV infusion. (No further information described in the paper)	Three SC infusions and three IV infusion. No data on how long many days this took.	90 in each group. (6 infusions per participant¶)	No data

* No description of blinding / concealment

† Calculated based on number of participants per group x mean duration of intervention.

‡ Calculated based on number of participants per group x two infusion per day x two days of infusions.

§ Number of infusions calculated by number of participants x 1.5 per day per group.

¶ Calculated based on number of infusions divided by number of participants

Abbreviations: RCT: Randomized controlled trial, SC: Subcutaneous, IV: Intravenous, G: Gauge

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.[15]

* For judgement of the individual domains see Supplementary Text 4.1. For answer to signiling questions see Supplementary Text 4.7.

† For judgement of the individual domains see Supplementary Text 4.2. For answer to signiling questions see Supplementary Text 4.8.

‡ For judgement of the individual domains see Supplementary Text 4.3. For answer to signiling questions see Supplementary Text 4.9.

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.[15]
§ For judgement of the individual domains see Supplementary Text 4.4. For answer to signiling questions see Supplementary Text 4.10
¶ For judgement of the individual domains see Supplementary Text 4.5. For answer to signiling questions see Supplementary Text 4.11.
** For judgement of the individual domains see Supplementary Text 4.6. For answer to signiling questions see Supplementary Text 4.12.

Supplementary Text S3. Extracted study characteristics

3.1 Randomized studies

Challiner 1994 (24)

Methods

Publication type: Journal article
Study design: Randomized controlled trial - Open label
Country of study: England
Language of publication: English
Year of study: No data
Source of funding: No data
Aim of study: Efficacy of hypodermoclysis ("The aim of our study was to find out if sub-cutaneous fluids are effective in restoring hydration in elderly stroke patients when used in routine clinical practice. Serum osmolality was chosen as the biochemical marker of hydration.")
Aim of intervention: Predetermined volume ("Patients were randomly allocated to receive 2 litres of isotonic dextrose- saline solution (each litre contains 30 mmol of sodium chloride and 40 g of glucose) per 24 hours via the subcutaneous or the intravenous routes.")
Sample size calculation: Yes, based on serum osmolality

Participants

Recruitment: Consecutive patients from Elderly care unit
Inclusion/exclusion criteria: Inclusion: Unable to take oral fluids because of impaired conscious level or dysphagia. Exclusion: acute myocardial infarction, any condition for which the study fluid regime would be inappropriate, unable to give consent.
Type of patient: Geriatric patients with acute stroke. Dehydrated (mean s-osmolality 296 mOsm/kg baseline). ("Thirty-four acute stroke patients admitted consecutively to the Elderly Care Unit and unable to take oral fluids because of impaired conscious level and/or dysphagia.")
Age: SC: Mean: 82.8, range: 69-93, IV: Mean: 84.2, range: 71-95
Setting: Hospital ("Elderly Care Unit")
Sex: Male: 23, Female: 11
Number of participants: SC: 17, IV: 17

Interventions

Two liters of fluid per 24 hours.
Intervention: Subcutaneous hydration ("Subcutaneous fluids were delivered through a 19 gauge 'butterfly' cannula sited by a nurse on the trunk, axillary, scapular or thigh areas.")
Comparator: Intravenous hydration (No further description in the paper)
Fluid type infused: A combination of NaCl and dextrose
Duration of intervention: 48 hours (as per protocol)
Number of infusions: 68 per group**
Infusion site duration: 48 hours
Use of hyaluronidase: Hyaluronidase when necessary ("As far as possible, medical and nursing staff ensured the fluids ran to time. Hyaluronidase was not used routinely but if the subcutaneous infusion ran behind time, 1,500 units of hyaluronidase were added to each litre bag of fluid.")

Outcomes

Adverse effects
Outcome definition: No list of adverse effects observed for. ("Any complications of the fluid therapy were noted.")
How was the outcome assessed: No data
Serum Osmolality
Outcome definition: Cleary defined
Unit of measurement: mOsm/kg. Reported as mean and standard diviation.
How was the outcome assessed: Blood sample analysis "Osmolality was measured using the Osmomat 030 (Clandon, UK)."
Baseline data was potentially relevantly different (299 mOsm/kg in SC group vs 293 mOsm/kg in IV group). In the paper they perform an analysis of covariance to allow for

	the difference in the baseline values. The data included in our meta-analysis is adjusted based on this analysis of covariance. **Death** **Outcome definition:** Cleary defined **How was the outcome assessed:** Death was not listed as a secondary outcome, but only listes as a reason for lost to follow up.
Notes	**Calculated based on number of participants per group x two infusion per day x 2 days of infusions. Unable to find active email of corresponding author.

Delamaire 1992 (25)

Methods	**Publication type:** Abstract **Study design:** Randomized controlled trial - Open label **Country of study:** France **Language of publication:** French **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety and efficacy of subcutaneous hydration. (Translation from French: "We compared these two techniques *(SC and IV)* in a randomized protocol by evaluating the feasibility, efficacy, safety and comfort of each") **Aim of intervention:** Predetermined volume **Sample size calculation:** No data
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** Elderly patients unable to drink and / or dehydrated with renal impairment. **Type of patient:** Geriatric patients (Described as elderly patients, No information on participants hydration status) **Age:** Mean: 83, SD: No data **Setting:** No data **Sex:** No data **Number of participants:** 30
Interventions	**Intervention:** SC hydration (no further description) **Comparator:** IV hydration (no further description) **Fluid type infused:** A combination of NaCl and glucose (Translation from French: "2.5% NaCl + 4.5 g glucose" **Duration of intervention:** Mean: 7 days, SD: No data **Number of infusions:** 105** per group **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data **Death** **How was the outcome assessed:** Death was not listed as an outcome in the paper.
Notes	**Calculated based on number of participants per group x mean duration of intervention Unable to find active email of corresponding author.

Esmeray 2018 (26)

Methods	**Publication type:** Journal article **Study design:** Randomized controlled trial, crossover design - Open label **Country of study:** Turkey **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety and efficacy of subcutaneous hydration.

Aim of intervention: Clinical indication ("For each administration, 1000 ml of 09% salin solution was used after prescription by doctor.")
Sample size calculation: No data

Participants

Recruitment: Patients was recruited from a private long-stay geriatric unit
Inclusion/exclusion criteria: Inclusion: Age >65 years, daily fluid intake <1000 ml, mild/ moderate dehydrated or risk of dehydration, insufficient fluid intake. Exclusion: infection, acute dehydration, skin problems, IV medication or nutrition.
Type of patient: Geriatric patients ("Patients have Alzheimer's or other types of dementia ", "60% were dependent for fluid intake support.", No further information on participants hydration status)
Age: Mean: 81.97, SD: 8.81
Setting: Long-term care. ("private long-stay geriatric care unit")
Sex: Male: 3, Female: 27
Number of participants: 30

Interventions

Intervention: SC hydration ("21–23-gauge SC infusion butterfly needles.")
Comparator: IV hydration (No further information described in the paper.)
Fluid type infused: NaCl
Duration of intervention: 3 SC infusions and 3 IV infusion. No data on how long many days this took.
Number of infusions: SC: 90, IV: 90
Infusion site duration: SC mean: 32 hours, IV mean: 15 hours
Use of hyaluronidase: No data

Outcomes

Adverse effects
Outcome definition: An insufficient description of adverse effects observed for.
Study description of adverse effects observed for: "Administration monitoring form had several sections. One section collected data on edema, redness, bleeding and agitation that could develop during or after infusion practices."
How was the outcome assessed: Nurse from a different institute.
Time requirement of initiation:
Outcome definition: Cleary defined
Unit of measurement: Minutes
How was the outcome assessed: Study assessor

Notes

The study reports a very high frequency of patients with Redness and Bleeding (74% and 73% respectively) in the IV group. This high frequency is not mentioned in the discussion. Giving us reason to believe that it is either a reporting error or doublet entry for the same adverse effect. We have treated data as doublet entry and removed half of the events from all analysis.
Author contacted by email for missing data but no reply.

Luk 2008 (27)

Methods

Publication type: Letter to the editor
Study design: Open Randomized controlled trial
Country of study: China
Language of publication: English
Year of study: 2002-2005
Source of funding: Tung Wah Group Hospitals Research Fund
Aim of study: Safety and efficacy of subcutaneous hydration.
Aim of intervention: Clinical indication
Sample size calculation: No data

Participants

Recruitment: No data
Inclusion/exclusion criteria: Elderly patients age >65 years
Type of patient: Geriatric patients with "mild to moderate dehydration requiring parenteral fluid supplementation or were unsafe to feed orally."
Age: Mean: 85, Range: 66-104
Setting: Hospital

	Sex: Male: 34, Female: 23 **Number of participants:** SC: 29, IV: 28
Interventions	**Intervention:** SC hydration ("Hypodermoclysis was performed using a 22-gauge butterfly needle inserted into the subcutaneous tissue at a 30º angle to the skin surface.", "The lateral low aspect of the abdomen was chosen as the site for infusion.") **Comparator:** IV hydration ("For intravenous hydration, Angiocaths with 18 to 22 gauges were employed") **Fluid type infused:** NaCl, A combination of NaCl and glucose **Duration of intervention:** Up to 3 days **Number of infusions:** Unable to calculate **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**<u>Adverse effects</u>** **Outcome definition:** Clear description, with a list of adverse effects observed for and definitions of these. Study description of adverse effects observed for: "the infusion sites of both groups were carefully inspected for local complications such as redness, cellulitis, large localized collections of oedema (>10- cm diameter), pain, and haematoma." **How was the outcome assessed:** No data
Notes	Author contacted by email for missing data but no reply.

Noriega 2014 (30)

Methods	**Publication type:** Journal article **Study design:** Randomized controlled trial **Country of study:** Spain **Language of publication:** Spanish **Year of study:** 2012-2013 § **Source of funding:** No external funding § **Aim of study:** Efficacy of subcutaneous hydration **Aim of intervention:** Clinical indication (Translation from Spanish: "The intervention consisted of the administration of up to 1.5 l per day per route with the objective of rehydration via SC vs. IV.") **Sample size calculation:** Yes*
Participants	**Recruitment:** All patients admitted to acute geriatric unit was assessed for eligibility. **Inclusion/exclusion criteria:** Inclusion: Clinical dehydration based on biochemical markers, need for parenteral fluid. Exclusion: Hemodynamic unstable, need for more than 2 L of fluid per day. **Type of patient:** Geriatric patients, dehydrated (mean s-osmolality 327 mOsm/kg, mean s-urea 108 mg/dl, mean s-creatinine 1.9 mg/dl at baseline). **Age:** Mean: 85.4, SD: 7.6 **Setting:** Hospital, Unit of Acute Geriatrics at Hospital General de Granollers, Spain **Sex:** Male: 35, Female: 32 **Number of participants:** 34 (SC), 33 (IV)
Interventions	Up to 1.5 liters of fluid per 24 hours. **Intervention:** SC hydration (Translation from Spanish: "The sites authorized for subcutaneous infusion were the inner thighs, the lateral abdominal wall and the scapular region (supra and interscapular)", "…21 to 25 gauge (G) gauge needle needles were used…" **Comparator:** IV hydration (Translation from Spanish: "The authorized sites for IV infusion were the back of the hand, forearm and elbow flexion, avoiding damaged and / or irradiated areas of the skin as much as possible. Abbocath® 20-24 G caliber catheters were used") **Fluid type infused:** NaCl, 5% dextrose, a combination of NaCl and dextrose **Duration of intervention:** 3 days, Predetermined duration **Number of infusions:** ** 102 in SC group, 99 in IV group

	Infusion site duration: No data, Numbers of catheters use: SC: 1.21 ± 0.41; IV: 1.48 ± 0.62. **Use of hyaluronidase:** No use of hyaluronidase §
Outcomes	**Adverse effects** **Outcome definition:** An insufficient description of adverse effects observed for. Study description of adverse effects observed for: Translation from Spanish: "Daily observations were made by researchers…the presence of adverse effects (extravasation, edema and local infection), the need for replacement catheter…" **How was the outcome assessed:** Study Assessor **Serum osmolality** **Outcome definition:** Cleary defined **Unit of measurement:** mOsm/kg **How was the outcome assessed:** Blood sample analysis **Urea** **Outcome definition:** Cleary defined **Unit of measurement:** mg/dl **How was the outcome assessed:** Blood sample analysis **Creatinine** **Outcome definition:** Cleary defined **Unit of measurement:** mg/dl **How was the outcome assessed:** Blood sample analysis **Death** **Outcome definition:** Cleary defined **How was the outcome assessed:** Death was not listed as a secondary outcome, but only listes as a reason for lost to follow up.
Notes	*They describe a non-inferior intention but not a non-inferior sample size calculation. Further, we cannot reproduce the sample size calculation due to lack of variance on data. **Calculated based on number of participants per group x mean duration of intervention §Author able to supply some of the missing data.

O'Keeffe 1996 (28)

Methods	**Publication type:** Journal article **Study design:** Randomized controlled trial **Country of study:** UK **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety and Efficacy of hypodermoclysis ("The aim of this study was to compare the effectiveness and tolerance of the two methods of administering fluids in elderly patients with cognitive impairment") **Aim of intervention:** Clinical indication ("Up to 2 litres of fluid was permitted in any 24-hour period") **Sample size calculation:** Yes
Participants	**Recruitment:** Patients admitted to an acute geriatric unit **Inclusion/exclusion criteria:** Inclusion: Require parenteral fluids due to dehydration or poor intake and cognitive impairment. Exclusion: Require I.V. medication, more then 2L of fluid required per 24 hours, poor tissue perfusion. **Type of patient:** Geriatric patient with cognitive impairment (Mini-Mental Status Examinatio score of ≤ 20). Mild dehydration or poor oral intake (mean s-urea 28 mg/dl, mean s-creatinine 1.2 mg/dl at baseline) **Age:** Mean: 82.5, SD: 6.52 **Setting:** Hospital, acute geriatric unit. **Sex:** Male: 23, Female: 37 **Number of participants:** 60
Interventions	Up to 2 liters of fluid per 24 hours.

Intervention: SC ("Subcutaneous fluids were administered in the infraclavicular, scapular, abdominal or thigh areas through a 21-gauge 'butterfly' cannula sited by a doctor")
Comparator: IV ("Intravenous fluid were administred through and 18-20-gauge cannula in the forearm vains")
Fluid type infused: NaCl, 5% dextrose, a combination of NaCl and dextrose. These was acceptable fluids, no data on administered fluids.
Duration of intervention: 48 hours (predetermined)
Number of infusions: SC: 90, IV: 90**
Use of hyaluronidase: No use of hyaluronidase

Outcomes

Adverse effects
Outcome definition: No list of adverse effects observed for.
How was the outcome assessed: Nursing staff
Agitation
Outcome definition: "Presence of agitated bahaviour (using a modification of the Cohen-Mansfield Agitation Inventory.)"
How was the outcome assessed: Nursing staff
Death
Outcome definition: Cleary defined
How was the outcome assessed: Death was not listed as a secondary outcome, but only listes as a reason for lost to follow up.

Notes

One patient was switched to SC because of difficulties with venous access. This patient is excluded in the article but included in the meta-analysis as "Need of resetting of infusion needle".
**Number of infusions calculated by number of participants x 1.5 per day (base on the volume of infused fluid) per group.
Author contacted by email for missing data but no reply.

Slesak 2003 (29)

Methods

Publication type: Journal article
Study design: Randomized controlled trial
Country of study: Germany
Language of publication: English
Year of study: 2001-2002
Source of funding: No external funding. §
Aim of study: Safety and efficacy of hypodermoclysis, patient's acceptance.
Aim of intervention: Clinical indication. Volume of fluid therapy depended on the medical necessity (maximum volume given was 1.5 l per day in both groups.)
Sample size calculation: Yes, based on patients, nurses and doctor's assessment of score.

Participants

Recruitment: Admitted to geriatric department
Inclusion/exclusion criteria: Inclusion: Receiving parenteral fluid. Exclusion: >60 years of age, General edema, skin disease, fluid regime inappropriate, IV drug administration.
Type of patient: Geriatric patients, with signs of mild to moderate dehydration (median s-creatinine 1.0 mg/dl; 88). ("Patients aged 60 and older presenting with signs of mild to moderate dehydration needing parenteral fluids on admission or during their stay in the geriatric department were enrolled in the study.")
Age: Mean: 85.3 years, SD: 6,7
Setting: Hospital, geriatric wards in the Geriatric Department
Sex: Male: 29, Female: 67
Number of participants: SC: 48, IV: 48

Interventions

Up to 1.5 liters of fluid per 24 hours.
Intervention: SC ("Nurses followed the hospital's standard guidelines for SC infusions (butterfly 21 gauge (G)), in SC tissue of thigh, abdomen, or thorax.")
Comparator: IV ("Doctors put in place peripheral IV catheters (size 22 G to 18 G")

Fluid type infused: A combination of NaCl and glucose, Ringer lactate., "Fluids were given by bolus infusion of 500 mL within 2 to 6 hours. The amount and duration of fluid therapy depended on the medical necessity."
Duration of intervention: SC: Median: 6, range 1;36 days. IV: Median: 6, range 1;32 days.
Number of infusions: SC: 288, IV: 288**
Infusion site duration: SC: median 2.0 range: 0.5;9, IV median: 2.8, range: 0.3-8.8 days
Use of hyaluronidase: Hyaluronidase used when deemed necessary

Outcomes

Adverse effects
Outcome definition: Clear description.
Study description of adverse effects observed for: "Nursing staff and doctors thoroughly observed adverse reactions and wrote them down in a standardized form. Localized adverse effects were categorized into two groups: measuring more or less than 10 cm in diameter" Listed adverse effects: Acute cardiac failure, Hyponatremia, Large edema, Large erythema, Cellulitis, Large phlebitis, severe pain, Leakage/paravesal, Minor erythema, Minor edema, Slight pain, Minor hematoma, Cannula plugged, Minor phlebitis, Itching.
How was the outcome assessed: "Nursing staff and doctors thoroughly observed adverse reactions and wrote them down in a standardized form."
Time requirement of initiation
Outcome definition: Cleary defined
Unit of measurement: Minutes. Reported as median and range.
How was the outcome assessed: Study assessor
Creatinine
Outcome definition: Cleary defined
Unit of measurement: mg/dl. Reported as median and quantile. Missing data on some patients. No reason listed.
How was the outcome assessed: Blood sample analysis
Volume infused
Outcome definition: Clearly defined
Unit of measurement: ml per day***

Notes

**Calculated based on number of participants per group x mean duration of intervention.
*** Reported as median and range. In meta-analysis data have been converted to mean and sd by median = mean and sd = range / 4
§ Additional information requested and supplied from author.

3.2 Non-randomized studies

Arinzon 2004 (33)

Methods

Publication type: Journal article
Study design: Cross sectional prospective
Country of study: No data
Language of publication: English
Year of study: 2001-2002
Source of funding: No data
Aim of study: Safety and efficacy of hypodermoclysis
Aim of intervention: Clinical indication
Sample size calculation: No data

Participants

Recruitment: Patients in three long term wards
Inclusion/exclusion criteria: Received hypodermoclysis
Type of patient: Geriatric patients
Age: Mean: 78.2, SD: 7.2
Setting: Long-term care

	Sex: Male: 6, Female: 51 **Number of participants:** 57
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** NaCl + a combination of NaCl and dextrose **Duration of intervention:** No data **Number of infusions:** 180 **Infusion site duration:** No data **Use of hyaluronidase:** No use of hyaluronidase
Outcomes	**Adverse effects** **Outcome definition:** Clear description. Study description of adverse effects observed for: "The adverse effects of fluid administration were also evaluated. These included: local reactions (e.g. swelling, obstruction, redness or inflammation), complaints of discomfort or pain and fluid overload (such as signs of exacerbation of congestive heart failure)." **How was the outcome assessed:** No data
Notes	Unable to find active email of corresponding author.

Bigot 2013 (32)

Methods	**Publication type:** Abstract **Study design:** Cross sectional prospective **Country of study:** France **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** No data **Sample size calculation:** No data
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** No data **Type of patient:** Geriatric patient **Age:** No data **Setting:** Hospital **Sex:** No data **Number of participants:** 115
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** No data, Drugs was added to the infusion in 14.7% of cases. **Duration of intervention:** No data **Total number of infusions:** Unable to calculate total number of infusions. **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	Author contacted by email for missing data and possible full text article but no reply.

Bruera 1990 (44)

Methods	**Publication type:** Journal article **Study design:** Cross sectional retrospective **Country of study:** Canada **Language of publication:** English **Year of study:** 1988 **Source of funding:** No external funding§

	Aim of study: Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** Consecutive patients admitted to palliative care unit **Inclusion/exclusion criteria:** Require parenteral hydration **Type of patient:** Terminal patients **Age:** Mean age: 62, SD: 14 **Setting:** Hospital **Sex:** Male: 21, Female: 37 **Number of participants:** 58
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** A combination of NaCl and dextrose, KCl was added to all infusions, mean daily dose of KCl was 25 ±8 mEq, Morphine and hydromorphone was added to some of the infusions. **Duration of intervention:** Mean: 14 days, SD 9 **Number of infusions:** 812** **Infusion site duration:** Mean: 4, SD: 3 **Use of hyaluronidase:** All interventions with hyaluronidase
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. The paper does not describe adverse effects during infusion, but only reason for discontinuation. **How was the outcome assessed:** No data
Notes	§ Additional information requested and supplied from author. **Calculated based on number of participants x mean duration of intervention

Bruera 1996 (43)

Methods	**Publication type:** Journal Article **Study design:** Cross sectional retrospective **Country of study:** Canada **Language of publication:** English **Year of study:** 1991 and 1993 **Source of funding:** No external funding§ **Aim of study:** Volume of fluid infused **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** Consecutive patients **Inclusion/exclusion criteria:** All patients receiving SC hydration **Type of patient:** Terminal patients **Age:** Mean: 63, SD 14 **Setting:** Hospital **Sex:** Male: 85, Female: 118 **Number of participants:** 203
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None* **Fluid type infused:** NaCl, A combination of NaCl and dextrose **Duration of intervention:** Mean: 12, SD: 8 **Number of infusions:** 2436** **Infusion site duration:** Mean: 5.2, SD: 2.8 **Use of hyaluronidase:** All interventions with hyaluronidase
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for.

	The study describes 62 patients needed to have the rate of infusions decreased because of site problems or the development of complete renal failure, but no further description. Data from this study is therefore not included in data syntheses. **How was the outcome assessed:** Chart review
Notes	Only patients from the Palliative care unit is included in this review as the authors could not determine if there was any complication in the patients in the cancer unit. *This study is a case-control comparing the volume of infused fluid between SC and IV. We have only included data from the SC group, as data on adverse effects was not available in the IV group. § Additional information requested and supplied from author. **Calculated based on number of participants x mean duration of intervention

Centeno 1999 (35)

Methods	**Publication type:** Letter to the editor **Study design:** Cross sectional prospective **Country of study:** Canada **Language of publication:** English **Year of study:** 1998 **Source of funding:** No external funding§ **Aim of study:** Efficacy without hyaluronidase **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** Consecutive patients admitted **Inclusion/exclusion criteria:** Requiring hypodermoclysis **Type of patient:** Terminal patients **Age:** No data **Setting:** Palliative care unit **Sex:** No data **Number of participants:** 24
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** NaCl + a combination of NaCl and dextrose **Duration of intervention:** Mean: 12 days, SD: 9 **Number of infusions:** 288** **Infusion site duration:** Mean: 3.3 days, SD: 5.4 **Use of hyaluronidase:** Hyaluronidase was use when deemed necessary. In 2/26 patients was it necessary to add hyaluronidase
Outcomes	**<u>Adverse effects</u>** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	**Calculated based on number of participants x mean duration of intervention § Additional information requested and supplied from author. Author able to supply some of the missing data.

Chalany 2015 (45)

Methods	**Publication type:** Journal article **Study design:** Cross sectional **Country of study:** Czech Republic **Language of publication:** Czech **Year of study:** 2012-2012 **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis

	Aim of intervention: Clinical indication **Sample size calculation:** N/A
Participants	**Recruitment:** Patients was recruited from a nursing home for patients with terminal dementia **Inclusion/exclusion criteria:** Terminal dementia **Type of patient:** Terminal dementia **Age:** Mean age: 78.8, SD 6.4 **Setting:** Geronto-psychiatric ward **Sex:** Male: 0, Female: 60 **Number of participants:** 60
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** NaCl **Duration of intervention:** Mean: 4.2 days, SD 2.6 **Number of infusions:** 252** **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** Clear description. Study description of adverse effects observed for: Translation from Czech: "Complication of subcutaneous rehydration were defined as the presence of local edema, local redness or symptoms of local infection at the site of needle puncture…" **How was the outcome assessed:** Nurse chart
Notes	**Calculated based on number of participants x mean duration of intervention Unable to find active email of corresponding author.

Dasgupta 2000 (31)

Methods	**Publication type:** Journal article **Study design:** Prospective Case-control **Country of study:** Canada **Language of publication:** English **Year of study:** 1998 **Source of funding:** No external funding§ **Aim of study:** Safety and efficacy of subcutaneous hydration **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** All patients matching inclusion during the study period. **Inclusion/exclusion criteria:** Inclusion: Received either SC or IV hydration. Exclusion: Received SC medication, only one SC infusion, received blood products, life-threatening conditions. **Type of patient:** Geriatric and cancer patients **Age:** Mean: 83.7, SD: 10.5 **Setting:** Long-term care **Sex:** Male: 15, Female: 40 **Number of participants:** 55
Interventions	**Intervention:** SC hydration **Comparator:** IV hydration **Fluid type infused:** A combination of NaCl and dextrose **Duration of intervention:** Mean: SC: 11.4, IV: 5.3, SD: SC: 9.8, IV: 2.6 **Number of infusions:** 807 in SC group, 106 in IV group **Infusion site duration:** No data **Use of hyaluronidase:** No use of hyaluronidase§
Outcomes	**Adverse effects**

	Outcome definition: Clear description. Study description of adverse effects observed for: "Adverse effects of fluid administration were evaluated. These included local catheter reactions (e.g., redness, obstruction, or swelling), patient discomfort (e.g., attempts by the resident to remove the catheter), and possible episodes of fluid overload (e.g., symptoms suggesting congestive heart failure for which furosemide therapy was prescribed, or for which the fluid infusion rate was decreased)." **How was the outcome assessed:** Study assessor
Notes	§ Additional information requested and supplied from author.

Fainsinger 1994 (36)

Methods	**Publication type:** Journal Article **Study design:** Cross sectional Prospective **Country of study:** Canada **Language of publication:** English **Year of study:** 1990-1991 **Source of funding:** No data **Aim of study:** To assess indication for SC **Aim of intervention:** Clinical indication **Sample size calculation:** N/A
Participants	**Recruitment:** Consecutive patients who died while admitted. **Inclusion/exclusion criteria:** Transferred or discharged were excluded. **Type of patient:** Terminal patients **Age:** Mean age: 66, SD: 13 **Setting:** Palliative care unit **Sex:** Male: 37, Female: 32 **Number of participants:** 69 patients received SC hydration
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, A combination of NaCl and dextrose **Duration of intervention:** Mean: 14 days, SD:18 **Number of infusions:** 966** **Infusion site duration:** Mean: 4.7 days, SD: 5.4 days. **Use of hyaluronidase:** All interventions with hyaluronidase
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** Study assessor
Notes	**Calculated based on number of participants x mean duration of intervention Author contacted by email for missing data but no reply.

Hussain 1996 (46)

Methods	**Publication type:** Journal article **Study design:** Cross sectional retrospective **Country of study:** USA **Language of publication:** English **Year of study:** 1992-1994 **Source of funding:** No data **Aim of study:** Safety and efficacy of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** All patients that received SC during the observation period **Inclusion/exclusion criteria:** Received SC

	Type of patient: Geriatric patients **Age:** Mean age: 85, SD: No data **Setting:** Long-term care **Sex:** Male: 10, Female: 26 **Number of participants:** 36
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, A combination of NaCl and dextrose **Duration of intervention:** Mean: 4 days, SD: No data **Number of infusions:** 144** **Infusion site duration:** "Sites were rotated after administration of each liter" **Use of hyaluronidase:** Hyaluronidase when deemed necessary (used in 78% of patients)
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** Study assessor
Notes	**Calculated based on number of participants x mean duration of intervention. Unable to find active email of corresponding author.

Justino 2013 (37)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** Brazil **Language of publication:** Portuguese **Year of study:** 2008-2009 **Source of funding:** No data **Aim of study:** Applicability of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** All patients connected with the Pain Care Department **Inclusion/exclusion criteria:** Received SC **Type of patient:** Cancer patients **Age:** Mean age: 61, Range: 22-95 **Setting:** Hospital, outpatient, patient home **Sex:** Male: 6, Female: 10 **Number of participants:** 16 patients included in study, only 5 received SC hydration the rest received subcutaneous medication.
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, A combination of NaCl and dextrose **Duration of intervention:** Mean: 10.16 days, Range: 1-55, data for all 16 patients **Number of infusions:** Unknown number of hydration infusions **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** Study assessor
Notes	Author contacted by email for missing data but no reply.

Kackielo 2000 (52)

Methods	**Publication type:** Abstract **Study design:** Case report **Country of study:** USA **Language of publication:** English **Year of study:** No data

Source of funding: No data
Aim of study: Safety of hypodermoclysis
Aim of intervention: N/A
Sample size calculation: N/A

Participants

Recruitment: N/A
Inclusion/exclusion criteria: N/A
Type of patient: Terminal patient
Age: 78
Setting: Hospital
Sex: Male
Number of participants: 1

Interventions

Intervention: SC
Comparator: None
Fluid type infused: No data
Duration of intervention: N/A
Infusion site duration: 3 days treatment prior to admission
Use of hyaluronidase: No data

Outcomes

Adverse effects
Outcome definition: N/A
How was the outcome assessed: Assessor

Notes

Unable to find email address of corresponding author.

LAMANDÉ 2004 (38)

Methods

Publication type: Journal article
Study design: Cross sectional prospective
Country of study: France
Language of publication: French
Year of study: 2002
Source of funding: No data
Aim of study: Safety of hypodermoclysis
Aim of intervention: Clinical indication
Sample size calculation: No data

Participants

Recruitment: All patients receiving SC in the unit was included.
Inclusion/exclusion criteria: All patients were included
Type of patient: Geriatric patients
Age: Mean: 85, SD: 7
Setting: Short-term and Long-term care
Sex: Male: 22, Female: 28
Number of participants: 50

Interventions

Intervention: SC
Comparator: None
Fluid type infused: NaCl, a combination of NaCl and glucose
Duration of intervention: Mean: 20 days, SD: 26
Number of infusions: 1426
Infusion site duration: Daily site change
Use of hyaluronidase: No data

Outcomes

Adverse effects
Outcome definition: An incomplete list of adverse effects observed for, but no definition of these.
Study description of adverse effects observed for: Translation from French: "…The following parameters were collected daily throughout the duration of the HDC: …and local tolerance (pain, hematoma, infection, edema, other). … For local tolerance, the collection was done through the patient interview and inspection of the injection site. The phenomena of intolerance could also be reported to the doctor by the caregiver."

	How was the outcome assessed: Patient interview and Assessor reported
Notes	Unable to find active email of corresponding author.

Lemeray 2012 (54)

Methods	**Publication type:** Journal article **Study design:** Case report **Country of study:** France **Language of publication:** French **Year of study:** 2012 **Source of funding:** No external funding§ **Aim of intervention:** Clinical indication **Aim of study:** Safety of hypodermoclysis **Sample size calculation:** N/A
Participants	**Type of patient:** Geriatric patient **Age: Mean age:** 90 **Setting:** Hospital **Sex:** 1 female
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** A combination of NaCl and glucose **Duration of intervention:** 3 hours **Infusion site duration:** N/A **Use of hyaluronidase:** No use of hyaluronidase§
Outcomes	**Adverse effects** **Outcome definition:** N/A **How was the outcome assessed:** No data
Notes	§ Additional information requested and supplied from author.

Martinez-Riquelme 2005 (39)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** England **Language of publication:** English **Year of study:** 2005 **Source of funding:** No data **Aim of study:** Efficacy of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** Short bowel and GI failure causing excessive fluid loss, No effect of conventional treatment, Adequate macronutrient status, **Type of patient:** GI failure patients **Age:** Mean age: 65.3, SD: 13.5 **Setting:** Home based treatment **Sex:** Male: 4, Female: 6 **Number of participants:** 10
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, A combination of NaCl and dextrose, 2-4 mmol Mg was added if Mg depletion was confirmed. **Duration of intervention:** Total duration was 3 months with 3-7 days treatment per week **Number of infusions:** Unable to calculate total number of infusions.

	Infusion site duration: No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	Author contacted by email for missing data but no reply.

Mongardon 2008 (51)

Methods	**Publication type:** Letter to the editor **Study design:** Case report **Country of study:** France **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** N/A
Participants	**Recruitment:** N/A **Inclusion/exclusion criteria:** N/A **Type of patient:** Geriatric patient **Age:** 86 **Setting:** Hospital **Sex:** Female: 1 **Number of participants:** 1
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl **Duration of intervention:** Few hours **Infusion site duration:** N/A **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** N/A **How was the outcome assessed:** Assessor
Notes	Unable to find active email of corresponding author.

Sato 2008 (53)

Methods	**Publication type:** Journal Article **Study design:** Case report **Country of study:** Japan **Language of publication:** Japanese **Year of study:** 2007-2008 **Source of funding:** No data **Aim of study:** Efficacy of SC hydration **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** N/A **Inclusion/exclusion criteria:** N/A **Type of patient:** Geriatric patient **Age:** Mean: 85, range 78-90 **Setting:** Home care **Sex:** Male: 1, Female: 2 **Number of participants:** 3

Interventions	**Intervention:** SC hydration **Comparator:** None **Fluid type infused:** 5% glucose **Duration of intervention:** No data **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** N/A **How was the outcome assessed:** No data
Notes	Unable to find active email of corresponding author.

Schen 1981 (47)

Methods	**Publication type:** Journal article **Study design:** Cross sectional retrospective **Country of study:** Israel **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** No data **Type of patient:** Geriatric patients **Age:** Mean: 82, SD: No data **Setting:** Hospital, long-term care **Sex:** No data **Number of participants:** 634
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, 5% dextrose **Duration of intervention:** No data **Number of infusions:** 4500 **Infusion site duration:** No data **Use of hyaluronidase:** All infusions in hospital was with hyaluronidase, all infusions in long-term care was without.
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	Data from Schen 1981 Schen 1982 and Schen 1983 is expected to be from the same observational study and data is combined. Unable to find active email of corresponding author.

Schen 1982 (50)

Methods	**Publication type:** Letter to the editor **Study design:** Cross sectional retrospective **Country of study:** Israel **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** No data

	Inclusion/exclusion criteria: No data **Type of patient:** Geriatric patients **Age:** Mean: 82, SD: no data **Setting:** Hospital **Sex:** No data **Number of participants:** 67 (350 infusions)
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, 5% dextrose, up to 34 mmol/l of potassium was added if needed. **Duration of intervention:** No data **Infusion site duration:** No data **Use of hyaluronidase:** All interventions with hyaluronidase
Outcomes	
Notes	This article is an update/continuation of Schen 1981

Schen 1983 (48)

Methods	**Publication type:** Letter to the editor **Study design:** Cross sectional retrospective **Country of study:** Israel **Language of publication:** English **Year of study:** No data **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** No data **Type of patient:** Geriatric patient **Age:** No data **Setting:** Hospital and long-term care **Sex:** No data **Number of participants:** 634
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, 5% dextrose **Duration of intervention:** No data **Infusion site duration:** No data **Use of hyaluronidase:** All infusions in hospital was with hyaluronidase, all infusions in long-term care was without.
Outcomes	
Notes	This article is an update/continuation of Schen 1981

Torsheim 1999 (40)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** Norway **Language of publication:** Norwegian **Year of study:** No data **Source of funding:** No data **Aim of study:** Efficacy of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data

Participants	**Recruitment:** Patients admitted to palliation care unit was assessed for eligibility. No data on if all admitted patients was assess for eligibility. **Inclusion/exclusion criteria:** Inclusion: Dehydrated, ability to give consent. Exclusion: edema. **Type of patient:** Cancer patients **Age:** Mean: 73, SD: 7.5 **Setting:** Hospital, patient home **Sex:** Male: 5, Female: 4 **Number of participants:** 9
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl, 5% glucose **Duration of intervention:** 17 infusion in total, no data on duration **Infusion site duration:** No data **Use of hyaluronidase:** No use.
Outcomes	**Adverse effects** **Outcome definition:** Clearly described. Study description of adverse effects observed for. Translation from Norwegian: "Observations were recorded in a standardized observation form completed by the nurse. Any swelling in the subcutis was evaluated by measuring the diameter or circumferential increase of the stomach and thigh. Inflammation signs in cutis / subcutis were evaluated and documented with polaroid photo. Pain or other discomfort is recorded, with a description of location and character. If the infusion was interrupted, the cause should be stated in the form." **How was the outcome assessed:** Study assessor
Notes	Unable to find active email of corresponding author.

Vidal 2016 (41)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** USA **Language of publication:** English **Year of study:** No data **Source of funding:** No funding **Aim of study:** Safety and efficacy of hypodermoclysis, "To determine if caregivers were capable of administering SC" **Aim of intervention:** Predefined volume (1000 ml/day) **Sample size calculation:** No data
Participants	**Recruitment:** Patients included in a previous study on the relevance of hydration in the terminal patient could continue in this study. **Inclusion/exclusion criteria:** Having a caregiver that could administer SC fluid. **Type of patient:** Cancer patient **Age:** Median: 67, Range 60;78 **Setting:** Home based intervention **Sex:** Male: 11, Female: 10 **Number of participants:** 21
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** NaCl **Duration of intervention:** Up to 7 days **Infusion site duration:** No data **Number of infusions.** 120 **Use of hyaluronidase:** No data
Outcomes	**Adverse effects**

	Outcome definition: Clearly described. Study description of adverse effects observed for: "Caregivers received daily phone calls from research nurses to assess the following: …related issues including needle displacement, leakage, swelling, pain, discomfort, itching, bruising or any other problems, and the need for a research nurse visit. The caregiver rates the symptoms of swelling, discomfort, pain, redness, itch, bruising and others on a scale of 0 to 10, with 10 being the worst possible symptom and 0 no symptoms. For needle displacement and leakage, the answer was yes/no." **How was the outcome assessed:** Caregiver report / assessor observed
Notes	Author contacted by email for missing data but no reply.

Worobec 1997 (42)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** Canada **Language of publication:** English **Year of study:** 1995 **Source of funding:** No data **Aim of study:** Efficacy of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** Patients of a chronic care setting **Inclusion/exclusion criteria:** All patients receiving SC in the setting. **Type of patient:** Geriatric patient **Age:** Mean: 78, SD: 6.86 **Setting:** Long term-care **Sex:** Male: 4, Female: 8 **Number of participants:** 12
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** No data **Duration of intervention:** No data **Infusion site duration:** No data **Use of hyaluronidase:** All interventions with hyaluronidase
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** Patient file by assessor
Notes	Unable to find active email of corresponding author.

Yap 2001(49)

Methods	**Publication type:** Journal article **Study design:** Cross sectional retrospective **Country of study:** Singapore **Language of publication:** English **Year of study:** 2000 **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** All patients admitted was review **Inclusion/exclusion criteria:** All patients who received subcutaneous hydration **Type of patient:** Terminal patients **Age:** No data **Setting:** Hospice

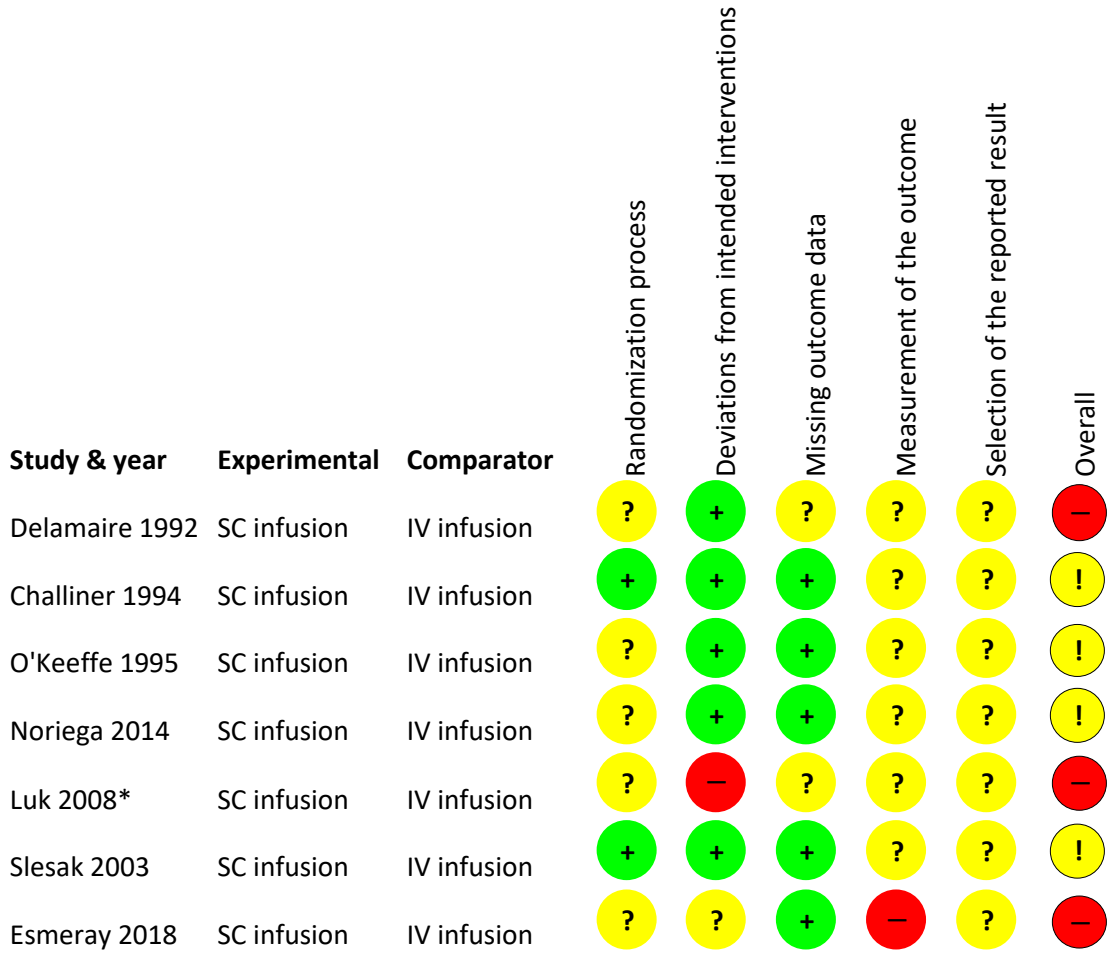
	Sex: No data **Number of participants:** 51
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** None **Fluid type infused:** 5% dextrose, A combination of NaCl and glucose/dextrose **Duration of intervention:** 5.49 days (mean), SD: 4.43 days,* **Number of infusions:** 290** **Infusion site duration:** 3.7 days* **Use of hyaluronidase:** No data *Calculated from information in article
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	*A total of 79 needles was inserted giving and mean infusion site duration of 3.7 days. **Calculated as one infusion per day Unable to find active email of corresponding author.

ŠŤASTNÁ 2009 (34)

Methods	**Publication type:** Journal article **Study design:** Cross sectional prospective **Country of study:** Czech Republic **Language of publication:** Czech **Year of study:** 2008 **Source of funding:** No data **Aim of study:** Safety of hypodermoclysis **Aim of intervention:** Clinical indication **Sample size calculation:** No data
Participants	**Recruitment:** Patients from a geriatric unit **Inclusion/exclusion criteria:** Requiring parenteral hydration with a difficult venous access **Type of patient:** Geriatric patient **Age:** Median: 83, Range: 56-96 **Setting:** Hospital **Sex:** Male: 20, Female: 41 **Number of participants:** 61
Interventions	**Intervention:** SC **Comparator:** None **Fluid type infused:** Plasma-Lyte **Duration of intervention:** Median: 4 days, range: 1-39 days **Number of infusions:** 425 **Infusion site duration:** No data **Use of hyaluronidase:** No data
Outcomes	**Adverse effects** **Outcome definition:** No list of adverse effects observed for. **How was the outcome assessed:** No data
Notes	Author contacted by email for missing data but no reply.

Supplementary Text S4. Risk of Bias 2. Judgement of individual domains.

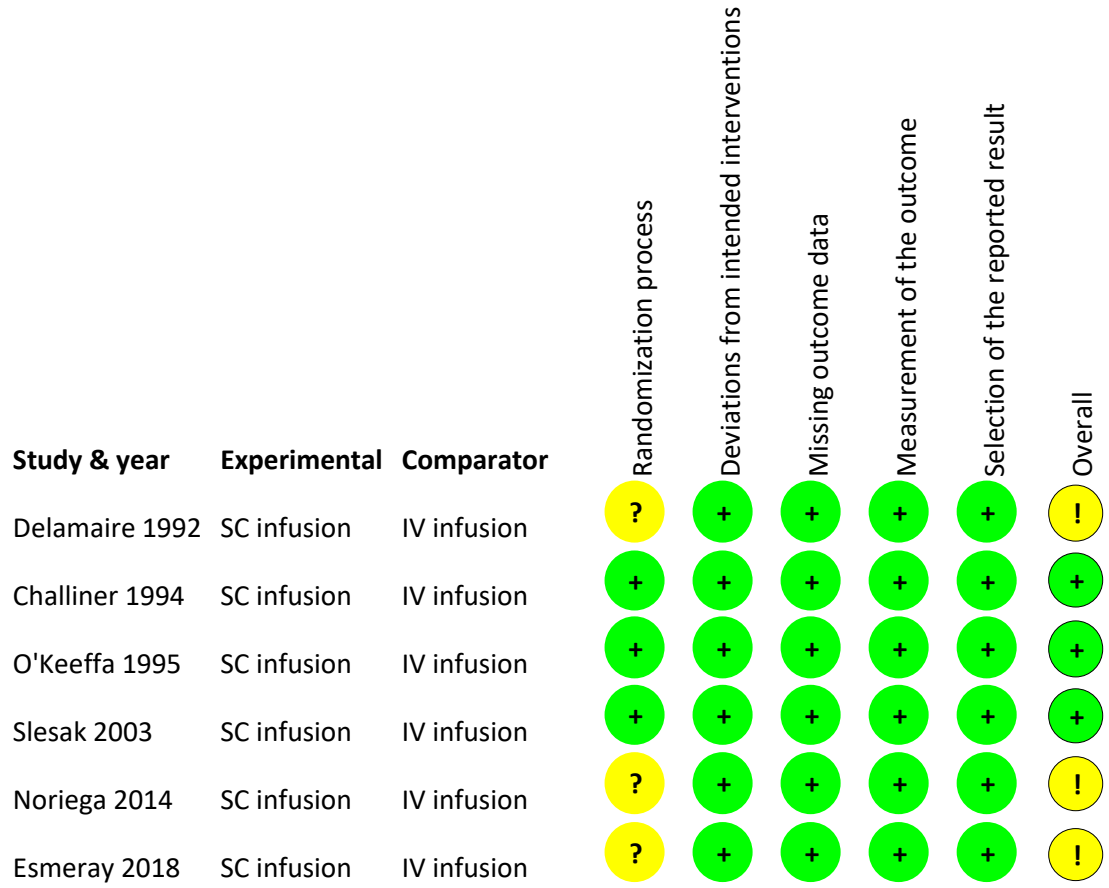
4.1 Outcome: Adverse effects



* Not included in the meta-analysis as data was not provided in a way so it could be included.

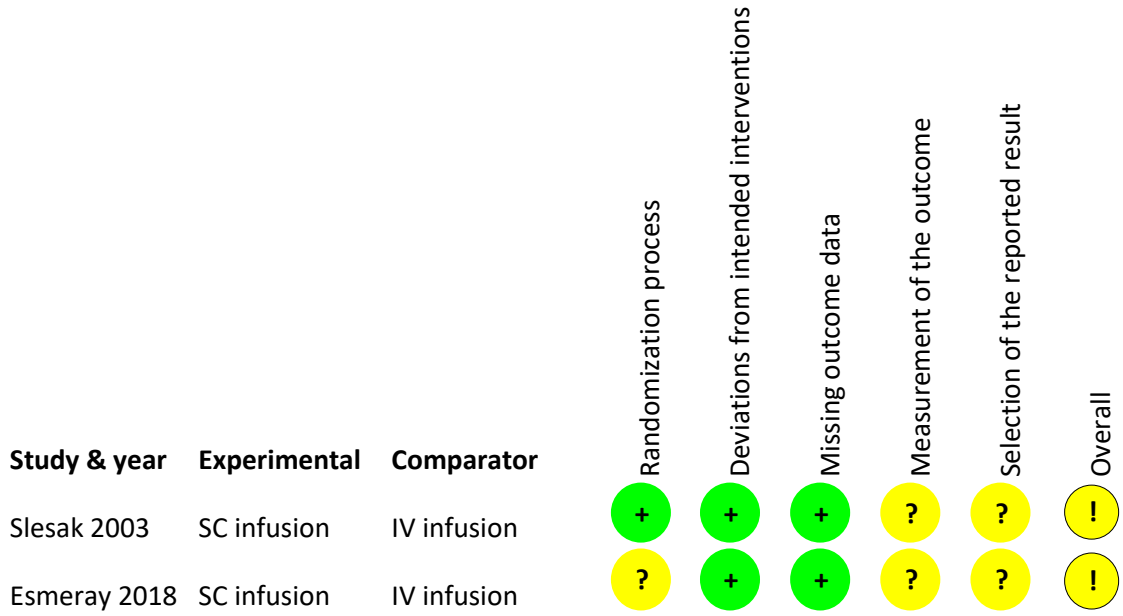
For response to signaling questions see Supplementary Text 4.7.

4.2 Outcome: Death



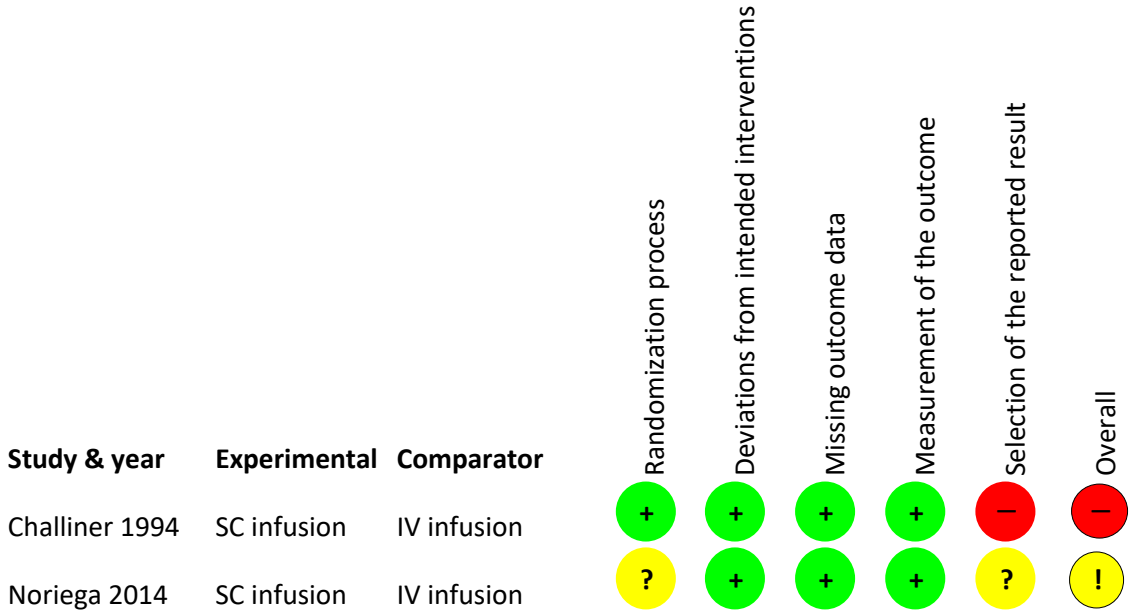
For response to signaling questions see Supplementary Text 4.8

4.3 Outcome: Catherter insertion time



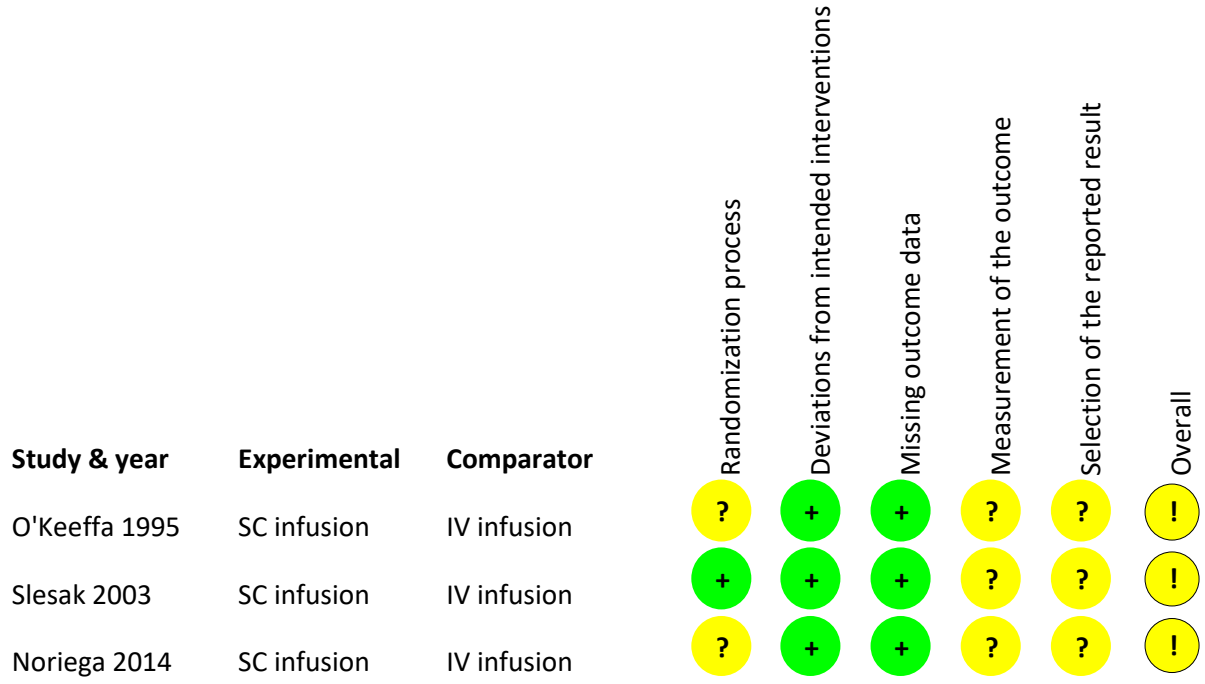
For response to signaling questions see Supplementary Text 4.9.

4.4 Outcome: Osmolality



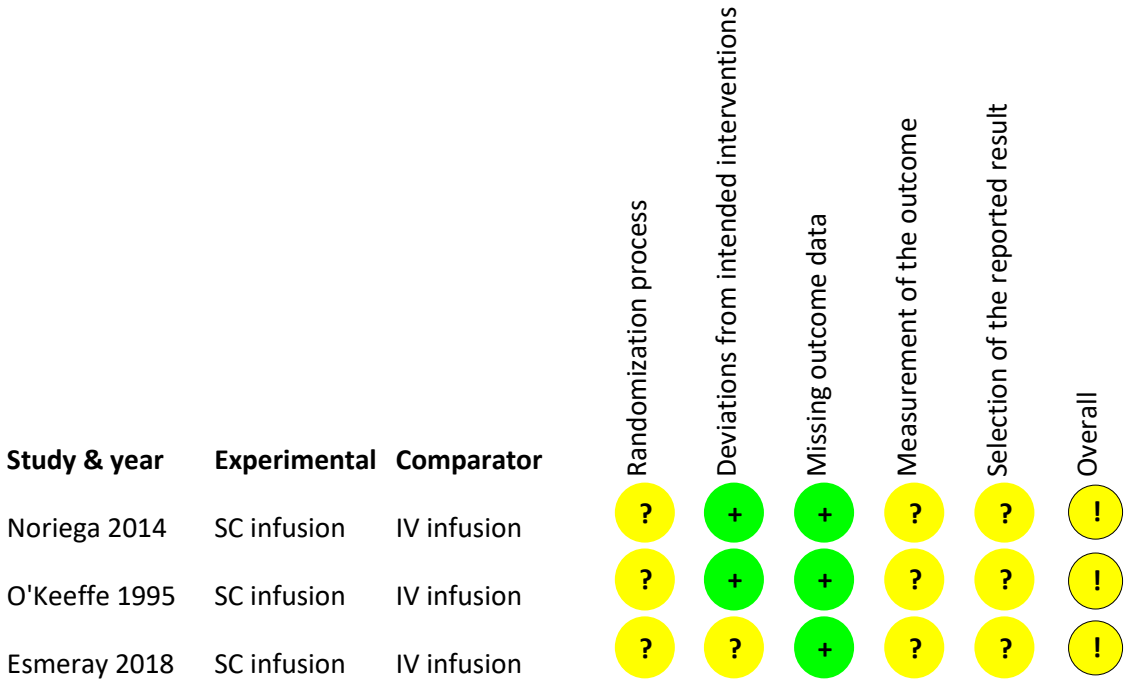
For response to signaling questions see Supplementary Text 4.10.

4.5 Outcome: Volume of fluid infused



For response to signaling questions see Supplementary Text 4.11.

4.6 Outcome: Agitation



For response to signaling questions see Supplementary Text 4.12.

4.7 Signaling questions for the outcome: Adverse effects

Unique ID	Challiner 1994	**Study ID**		**Assessor**	
Ref or Label	Challiner 1994	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Adverse effects	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Random treatment allocation was generated by computer, such that within each block of eight patients there were four patients on each treatment. These treatment allocations were transferred to sequentially numbered sealed envelopes which were opened by the junior doctor on call once he or she had decided the patient was eligible for the trial and consent had been obtained."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding and therefore very unlikely.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The paper does not perform statistical test on adverse effects. Signaling question answered as data are included in the meta-analysis.

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	No data on how many patients were observed for adverse effects, but as the patients were in-patients we expect they were observed. From method section: "Any complication of the fluid therapy were noted."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	Two patients excluded during the study but are re-included in our analysis
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	No description of which adverse effects were observed but probably ok as it is described that it was trained health care staff observing patients.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Both were internventions that required similar degree of observation
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	

Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Delamaire 1992	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Conference abstract(s) about the trial
Outcome	Adverse effects	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	The paper only describes patients being randomized but no additional informations is given.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No baseline data reported.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding for patients or caregivers
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The paper does not perform statistical test on adverse effects. Signaling question is answered as data are included in the meta-analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	No information on number of patients randomized.

	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Some concerns**	We don't know if patients were excluded after randomizations.
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	The methods section state that tolerance and complications are in focus as outcomes.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	As only sparse data is available we have judged the study to have some concerns in multiple domains in a way that substantially lowers confidence in the result.

Unique ID	Noriega 2014	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial

Outcome	Adverse effects	**Results**		**Weight**	
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			PY	Translations from spanish: "Randomization of treatment was performed by mixed blocks 6 sealed envelopes. Each block consisted of 3 cards with treatment 'IV' and 3 'SC'. The envelopes were opened after the patient's inclusion in the study and after obtaining informed consent." It might be possible to guess the allocation of the later envelopes depending on the previous allocations (page 104).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Table 1
	Risk of bias judgement			**Some concerns**	Based on 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	No description of blinding and therefore very unlikely.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	The paper does not perform statistical test on adverse effects. Signaling question answered as data is included in the meta-analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	

	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Numbers in tables is equal to randomized numbers, excluding those who died. Three patients died during the study. One 1 SC group and 2 in IV group. This is a sufficiently small fraction not to induce potential relevant bias.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Study description of adverse effects observed for: Translation from Spanish: "Daily observations were made by researchers…the presence of adverse effects (extravasation, edema and local infection), the need for replacement catheter…"
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	

Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	O'Keeffe 1995	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Adverse effects	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Allocation sequence generated by table of random numbers. Block randomization and sealed envelope. It might be possible to guess the allocation of the later envelopes depending on the previous allocations.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	Based 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding and therefore very unlikely. Caregivers described as assessors.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The paper does not perform statistical test on adverse effects. Signaling question answered as data is included in the meta-analysis.

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	One patient in i.v.-group excluded because of adverse effect (p.37). This event is re-included in our meta-analysis.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	No list of adverse effects described, but "nursing staff also note the presence of any ... disrutbance directly related to the infusion." (p.37)
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Slesak 2003	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Adverse effects	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Random treatment allocation was generated by mixing blocks of six sealed envelopes. Block size unknown to staff.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Described as an open trial.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	A total of 31% of patients switched intervention: 13/48 SC -> IV; 17/48 IV -> SC. This is according to protocol: "A switch of therapies was possible if medically or ethically indicated." (p.156, 2nd column, first two lines).
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Signaling question answered as data is included in the meta-analysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Although the paper does not describe specifically how many patients were observed for adverse effects we do not suspect a large number of missing data. The method section writes: "Nursing staff and doctors thoroughly observed adverse reactions and wrote them down in a standardized form." This had been designed and tested in a pilot phase. Data in table 2 and first paragraph on page 158 support complete reporting.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Nursing staff and doctors thoroughly observed adverse reactions and wrote them down in a standardized form."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.

	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Esmeray 2018	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Adverse effects	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Allocation sequence generated by "Random drawing method". No information on allocation concealment when including patients.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	1.4 Is a roughly equal proportion of participants allocated to each of the two groups?	Y	15 in each group.
	1.5 If N/PN/NI to 1.4: Are period effects included in the analysis?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	No description of blinding and therefore very unlikely. However, 67% of patients had dementia and were bedridden.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	

	2.5 Was there sufficient time for any carry-over effects to have disappeared before outcome assessment in the second period?	NI	No information on time between the two groups (wash-out period).
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Although the paper does not describe specifically how many patients were observed for adverse effects we have no grounds for suspecting a large number of missing data.
	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across interventions?	NA	
	3.3. If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Administration monitoring form had several sections. One section collected data on edema, redness, bleeding and agitation that could develop during or after infusion practices." "All administrations were performed on abdomen by the researcher, whereas the side effects were evaluated by a nurse, who came from a different institution, which connected of the institution."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**High**	Very high number of minor adverse effects in IV group compared to all other studies

			without any comment from the authors. We have treated some of the data as doublet entry and removed half of the events from all analysis. This will introduce bias in favor of the comparator (IV).
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	Luk 2008	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Adverse effects	**Results**		**Weight**	
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	"We carried out an open randomised controlled study". Insufficient information to evaluate quality of randomization.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	No baseline information is reported.
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	Study is described as an open trial. "We carried out an open randomised controlled study"
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	No information on how many patients did or did not recieved the assigned intervention.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI	It is not described what analysis were used. "Between the hypodermoclysis and intravenous groups, there were no significant differences in terms of percentage of patients with complications, catheter dislodgement and death."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NI	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	It is not described how many patients were observed for adverse effects. They state that "In some of the other patients the infusion was stopped prior to day 3" but not how many or from what group.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	Adverse effects could be a reason to stop the hydration treatment.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"For secondary outcomes, the infusion sites of both groups were carefully inspected" (p.49)
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Described as an open trial.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective outcome. Assessors conscious or unconscious preference for either method could influence the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Adequate number of what the authors consider adverse effects.
	5.3 ... multiple eligible analyses of the data?	NI	It is not described which analysis is used.
	Risk of bias judgement	**Some concerns**	Results report percentages while actual numbers are not provided.
Overall bias	**Risk of bias judgement**	**High**	

4.8 Signalling questions for the outcome: Death

Unique ID	Challiner 1994	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Deaths	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Random treatment allocation was generated by computer, such that within each block of eight patients there were four patients on each treatment. These treatment allocations were transferred to sequentially numbered sealed envelopes which were opened by the junior doctor on call once he or she had decided the patient was eligible for the trial and consent had been obtained."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	Blinding not described.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The paper does not present statistical test on death.

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Very likely that death was noticed as inpatients were observed repeatedly for clinical and biochemical outcomes.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	Low number of observations (n=1) with accurate reporting.
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	Delamaire 1992	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Conference abstract(s) about the trial
Outcome	Deaths	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	The paper only describes patients being randomized but no additional informations is given.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No baseline data reported.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	There is no information on concealment for patients or caregivers.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	The very limited description of methods causes some uncertainty.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	There is no information on missing data but there is no indication of lacking data and full reporting on this outcome is very likely.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	A very distinct outcome that cannot be misunderstood or neglecte knowingly or unknowingly.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	This outcome is solid.
Overall bias	**Risk of bias judgement**	**Some concerns**	Limited description of methods is an overall concern though the aims and outcomes are stated faily well and this outcome cannot be neglected.

Unique ID	Noriega 2014	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Deaths	**Results**		**Weight**	

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	N	Translations from spanish: "Randomization of treatment was performed by mixed blocks 6 sealed envelopes. Each block consisted of 3 cards with treatment 'IV' and 3 'SC'. The envelopes were opened after the patient's inclusion in the study and after obtaining informed consent."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Death is not reported as an outcome. It is listed that 3 patients died. Translated from spanish: "In the end, a total of 70 did not complete the follow-up due to death in the first 72 hours (one in the SC group and 2 in the IV group)."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	

	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Outcome distinct.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Outcome detailed for both groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	The data are provided in actual numbers.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	The raw data are available.
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	O'Keeffe 1995	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Number of Deaths	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Allocation sequence generated by table of random numbers.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	

			Block randomization. Sealed envelope.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	No description of concealment or sham.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Death is not reported as an outcome. It is only listed that 1 patient died: "...and 1 patient in the s.c. group died".
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	Death cannot be overlooked as confirmed by reporting of this outcome.
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	This outcome cannot be overlooked.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	Crude data are reported and very few. No analysis deemed necessary.
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	Slesak 2003	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Deaths	**Results**		**Weight**	
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Random treatment allocation was generated by mixing blocks of six sealed envelopes. Block size unknown to staff.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	Described as an open trial.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Missing data for other outcomes are described in detail. Death is not reportet probably due to survival of all participants.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	No deaths reported - all patients probably lived through the intervention.

Overall bias	**Risk of bias judgement**		**Low**	

Unique ID	Esmeray 2018	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Deaths	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Allocation sequence generated by "Random drawing method". No information on allocation concealment when including patients.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	1.4 Is a roughly equal proportion of participants allocated to each of the two groups?	Y	15 in each group.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No concealment described, but patients had dementia with 67% bedridden. Assessor came from a different institution but still no concealment of intervention described.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	We expect death to be reported.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	No events.
Overall bias	**Risk of bias judgement**	**Some concerns**	

4.9 Signalling questions for the outcome: Catheter insertion time

Unique ID	Slesak 2003	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Catheter insertions time	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Random treatment allocation was generated by mixing blocks of six sealed envelopes. Block size unknown to staff.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Described as an open trial.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Although the paper does not describe specifically how many patients data on insertion time is based on we do not suspect a

			large number of missing data.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	There is no description in the method section on how this outcome is collected. But "The ... time needed per cannula" sounds reasonable.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No description of statistical analysis plan or protocol is provided in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Esmeray 2018	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Catheter insertions time	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Allocation sequence generated by "Random drawing method". No information on allocation concealment when including patients.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	1.4 Is a roughly equal proportion of participants allocated to each of the two groups?	Y	15 in each group.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 Was there sufficient time for any carry-over effects to have disappeared before outcome assessment in the second period?	Y	No information on time between the two groups (wash-out period), but no wash-out is needed for this outcome.
	Risk of bias judgement	**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Although the paper does not describe specifically how many patients were observed for this outcome we do not suspect a large number of missing data. Data are provided for mean time spent on insertion of catheter, but lacking for number of insertions included in the calcualtion.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	There is no description in the method section on how this outcome is collected. But "Time spend for catheter ınsertion (minute)" sounds reasonable.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No description of statistical analysis plan or protocol is provided in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	

	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

4.10 Signalling questions for the outcome: Osmolality

Unique ID	Challiner 1994	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Osmolality / blood samples	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	"Random treatment allocation was generated by computer, such that within each block of eight patients there were four patients on each treatment. These treatment allocations were transferred to sequentially numbered sealed envelopes which were opened by the junior doctor on call once he or she had decided the patient was eligible for the trial and consent had been obtained."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	"An analysis of covariance was performed to allow for differences in

			baselines between the two groups. No statistical difference between the osmolalities of the two treatment groups was found (P = 0.12)."
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	"Not included in the analysis are two patients allocated to the subcutaneous group who dropped out of the study on Day 2: one died and one developed local oedema."
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Venous blood samples were collected into plain 'Vacutainer' tubes for measurement of serum urea, electrolytes, glucose and osmolality, on admission, prior to starting parenteral fluids (Day 1), and on Days 2 and 3 between 9 and 10 a.m. Osmolality was measured using the Osmomat 030 (Clandon, UK)." This is described as a standard laboratory procedure.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	It is unlikely that serum values can be

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	influenced by knowledge of treatment assignment.
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	The method section the paper describes serum urea, electrolytes were also collected, but despite these also are an indication for hydration status no description or analyses of this data is reported.
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**High**	The paper states the following:"The aim of our study was to find out if subcutaneous fluids are effective in restoring hydration in elderly stroke patients when used in routine clinical practice. Serum osmolality was chosen as the biochemical marker of hydration." Despite this statement, we judge the study to have a high risk of selective reporting bias.
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	Noriega 2014	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Osmolality / blood samples	**Results**		**Weight**	
Domain	**Signalling question**			**Response**	**Comments**

Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Translations from spanish: "Randomization of treatment was performed by mixed blocks 6 sealed envelopes. Each block consisted of 3 cards with treatment 'IV' and 3 'SC'. The envelopes were opened after the patient's inclusion in the study and after obtaining informed consent." It might be possible to guess the allocation of the later envelopes depending on the previous allocations (page 104).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1
	Risk of bias judgement	**Some concerns**	Based on 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding/concealment.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN	Three patients died during the study. One 1 SC group and 2 in IV group. This is a sufficiently small fraction not to induce potentially relevant bias.

			It is not described how many patients had data on Osmolality / blood samples available.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	No reason to suspect that data from patients were removed based on the value of the data.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Translation from Spanish: "The main efficacy variables of the hydration treatment were those established in previous studies as useful in hydration status monitoring: variations in urea, creatinine and serum osmolarity levels in serial measurements (in our study they were obtained 24 hours prior to inclusion and after 24, 48 and 72 h the start of treatment)."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	It is unlikely that serum values can be influenced by knowledge of treatment assignment.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

4.11 Signalling questions for the outcome: Volume of fluid infused

Unique ID	Noriega 2014	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Volume of fluid infused	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Translations from spanish: "Randomization of treatment was performed by mixed blocks 6 sealed envelopes. Each block consisted of 3 cards with treatment 'IV' and 3 'SC'. The envelopes were opened after the patient's inclusion in the study and after obtaining informed consent." It might be possible to guess the allocation of the later envelopes depending on the previous allocations (page 104).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1
	Risk of bias judgement	**Some concerns**	Based on 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Three patients died during the study. One 1 SC group and 2 in IV group. This is a sufficiently small fraction not to introduce potentially relevant bias.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Translation from Spanish: “Daily observations were made by researchers which stated the type of solution, the volume administered, ...”
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Fluid volume prescription and assessment may be unknowingly influenced by knowledge of the intervention.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	O'Keeffe 1995	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Volume of fluid infused	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Allocation sequence generated by table of random numbers. Block randomization and sealed envelope. It might be possible to guess the allocation of the later envelopes depending on the previous allocations.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	Based 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding/concelament .
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	One patient in each group excluded. This is insufficient to change the result.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	"Nursing staff noted the amount of fluid prescribed and the actual amount of fluid administred". No information on the accuracy of measuring method.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Fluid volume prescription and assessment may be unknowingly influenced by knowledge of the intervention.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Slesak 2003	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Volume of fluid infused	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Random treatment allocation was generated by mixing blocks of six sealed envelopes. Block size unknown to staff.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Described as an open trial.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	From method section: "A switch of therapies was possible if medically or ethically indicated." From results section: "The SC infusion was switched 13 times to IV... A switch from the IV method to the SC arm was made 17 times."

			A large number of switches but all according to protocol.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI	Although the paper does not describe specifically how many patients provided data for volumen of fluid infused there is no reason to suspect missing data of a magnitude that would markedly influence the results.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	No description on how this outcome was assessed, but it is reported as a volume per day as is appropriate.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Fluid volume prescription and assessment may be unknowingly influenced by knowledge of the intervention.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No statistical analysis plan or protocol is described in the paper.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	

Overall bias	**Risk of bias judgement**	**Some concerns**	

4.12 Signalling questions for the outcome: Agitation

Unique ID	Noriega 2014	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Agitation	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Translations from spanish: "Randomization of treatment was performed by mixed blocks 6 sealed envelopes. Each block consisted of 3 cards with treatment 'IV' and 3 'SC'. The envelopes were opened after the patient's inclusion in the study and after obtaining informed consent." It might be possible to guess the allocation of the later envelopes depending on the previous allocations (page 104).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Table 1
	Risk of bias judgement	**Some concerns**	Based on 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Signallyng question answered as data are included in the metaanalysis.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Percentages in analysis on p.106 match the number of included
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Evaluation of clinical status, pharmacological and physical restrains. Translation from spanish: "The presence of psyhomotor agitation was documented by regular monitoring of physical and / or pharmacological restraint."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Assessors evaluation could have been influenced by a preference knowingly or unknowingly
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No description of a prespecified analysis plan
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	

Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	O'Keeffe 1995	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Agitation	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Allocation sequence generated by table of random numbers. Block randomization and sealed envelope. It might be possible to guess the allocation of the later envelopes depending on the previous allocations.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	Based 1.2
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	No description of blinding. Caregivers = assessors
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	As evaluated from table 1
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	p. 38, as evaluated from calculations. One patient from each group was excluded from the analysis, but this is too limited to alter the results.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Citing from page37, first column: "Before randomization, the doctor recorded the presence of absence of agitated behaviour (using a modification of the Cohan-Mansfield Agitation Inventory) based on his own observations and on discussions with nurses or carers regarding the behaviour of the subject during the previous 48 h." Citing from page37, second column: "Nursing staff also noted the presence of any agitation or distrubance directly related to the infusion."
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Subjective evaluation with the inherent risk in an open label trial of unkowingly favouring one intervention.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No prespecified analysis plan described.

	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	Esmeray 2018	**Study ID**		**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	SC	**Comparator**	IV	**Source**	Journal article(s) with results of the trial
Outcome	Agitation	**Results**		**Weight**	

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	Allocation sequence generated by "Random drawing method". No information on allocation concealment when including patients.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	1.4 Is a roughly equal proportion of participants allocated to each of the two groups?	Y	15 in each group.
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	No description of blinding but 67% were demented and bedridden
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 Was there sufficient time for any carry-over effects to have disappeared before outcome assessment in the second period?	NI	No information on the time between the two groups (wash-out period).
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	No reason to suspect missing of a marked number of data
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	"Administration monitoring form had several section. One section colledcted data on edema, redness, bleeding and agitation that could develop during or after infusion practices." No further definition of agitation is provided, but assessors were trained staff with recordings on the monitoring form.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Knowingly or unknowingly preference for either method could influence evaluation.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	The paper proveds no description of protocol or analysis plan.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	

Overall bias	**Risk of bias judgement**	**Some concerns**	

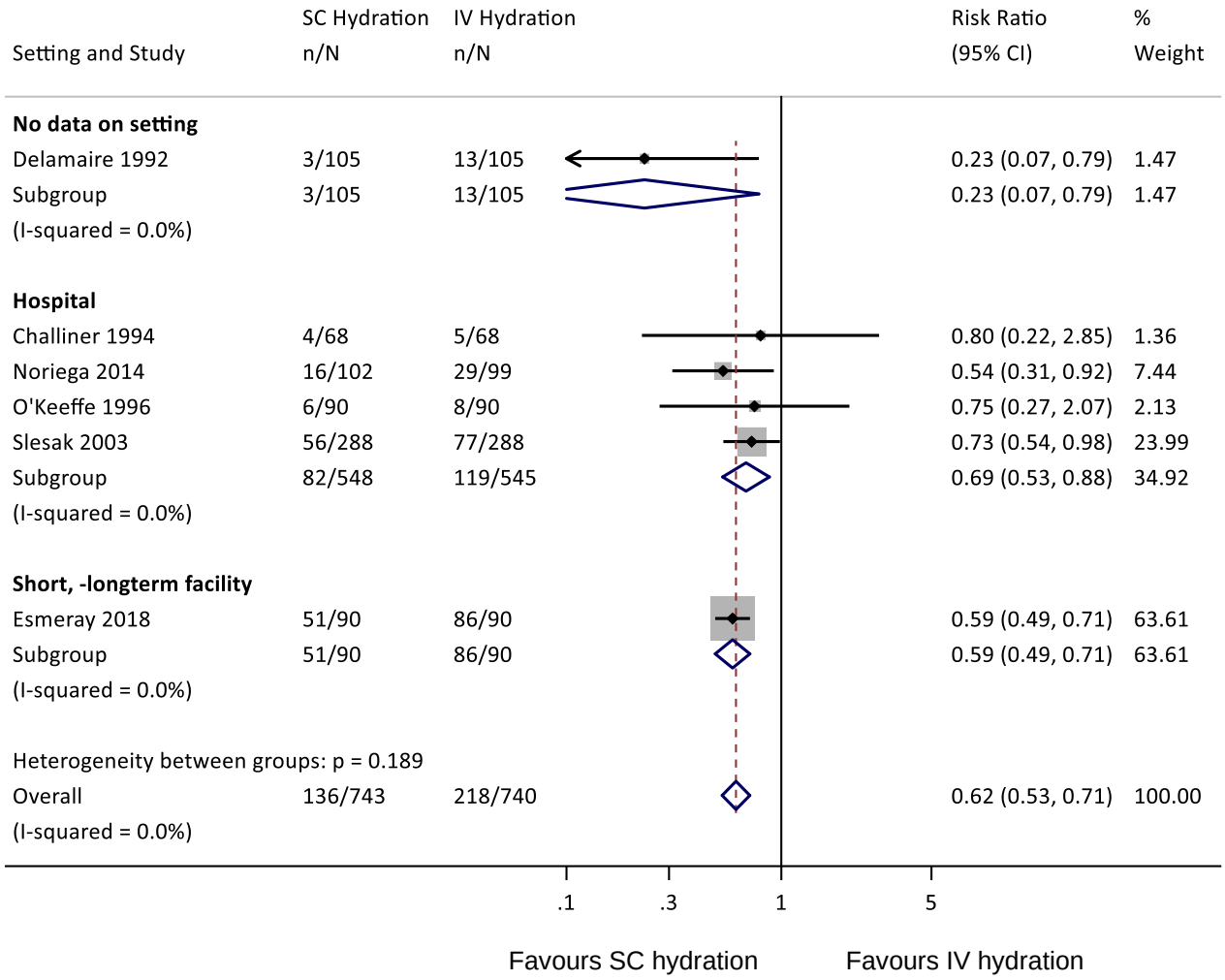
Supplementary Table S2. Risk of bias of cross-sectional studies for the outcome of adverse effects

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

[a]Further information on adverse effects description of included studies can be found in Supplementary Text S3. Extracted study characteristics.
[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:

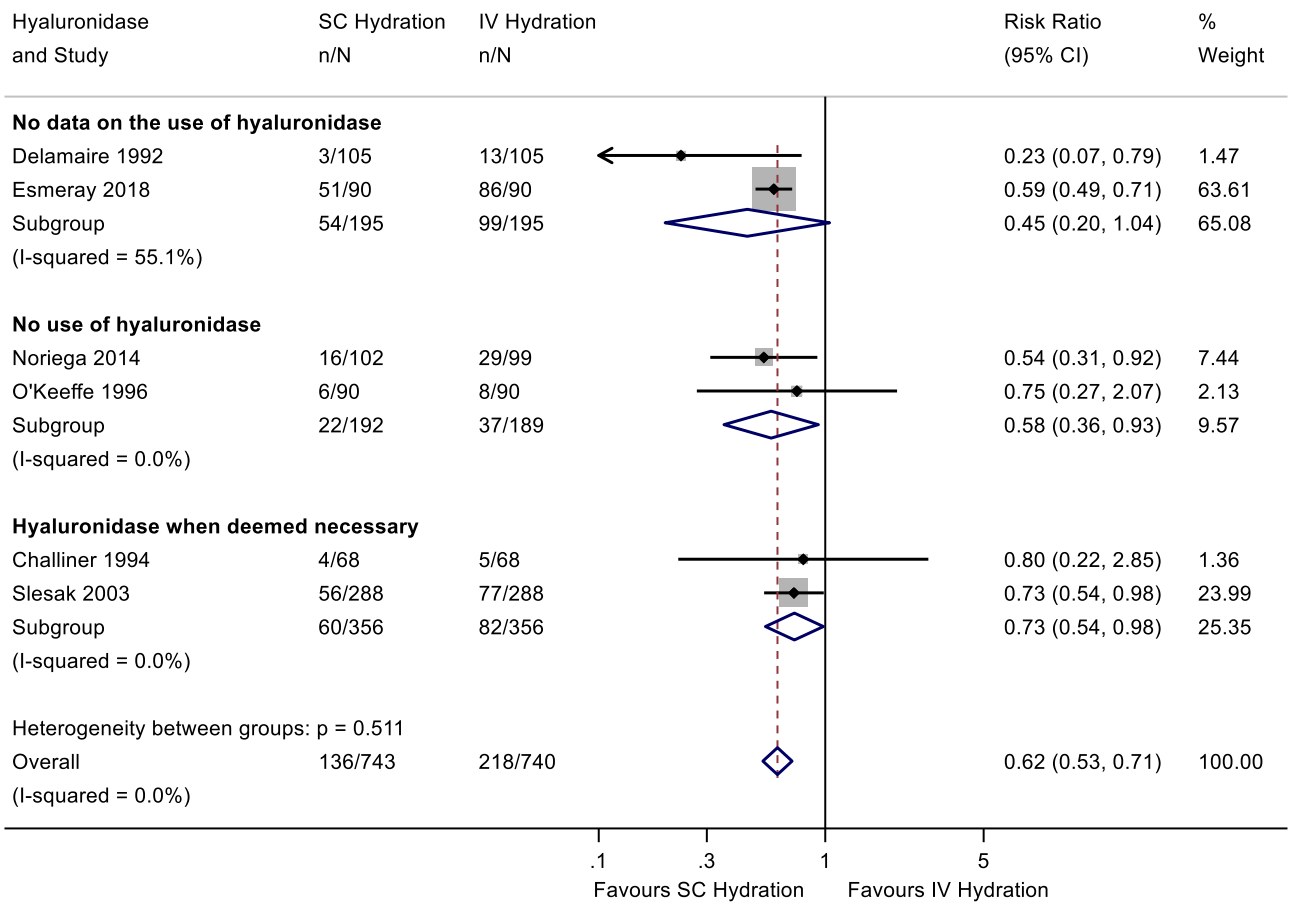
No data on setting	z = -2.344 p = 0.019
Hospital	z = -2.950 p = 0.003
Short, -longterm facility	z = -5.504 p > 0.00001
Overall	z = -6.417 p > 0.00001

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:

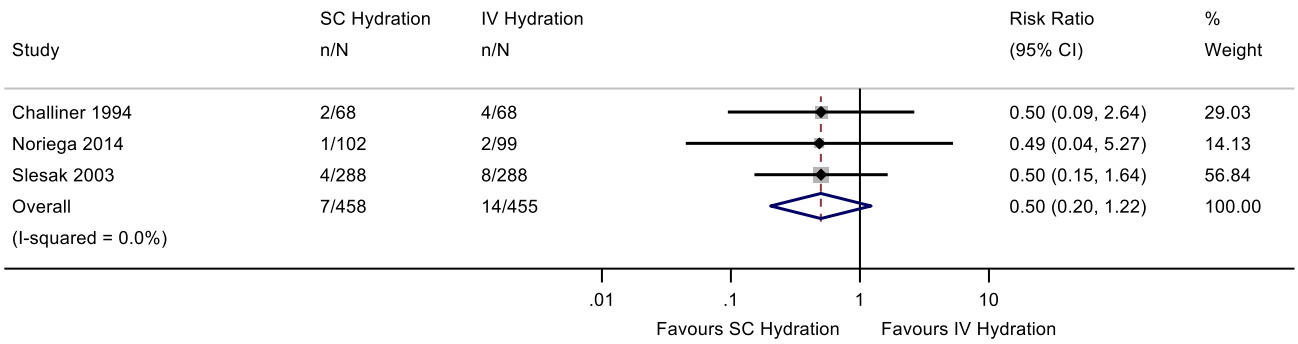
No data on the use of hyaluronidase	z = -1.858	p = 0.063
No use of hyaluronidase	z = -2.245	p = 0.025
Hyaluronidase when deemed necessary	z = -2.084	p = 0.037
Overall	z = -6.417	p > 0.00001

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.



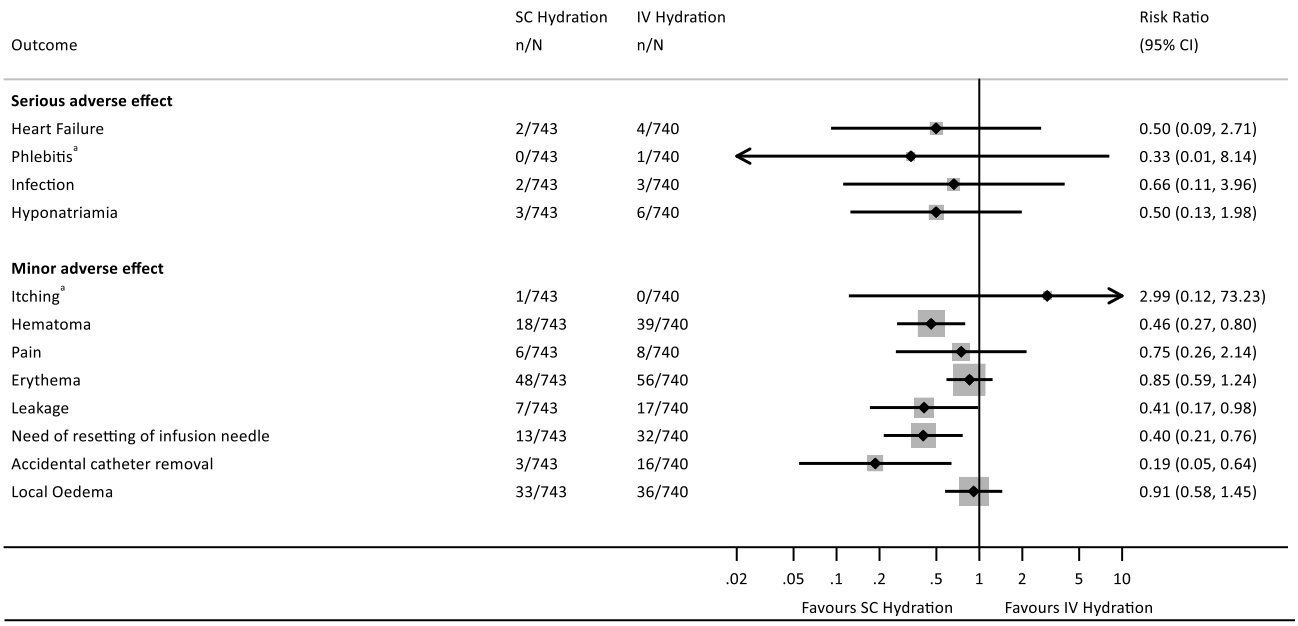
Both-armed zero-event (BA0E) excluded due to the choice of DerSimonian-Laird random effects model.

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		

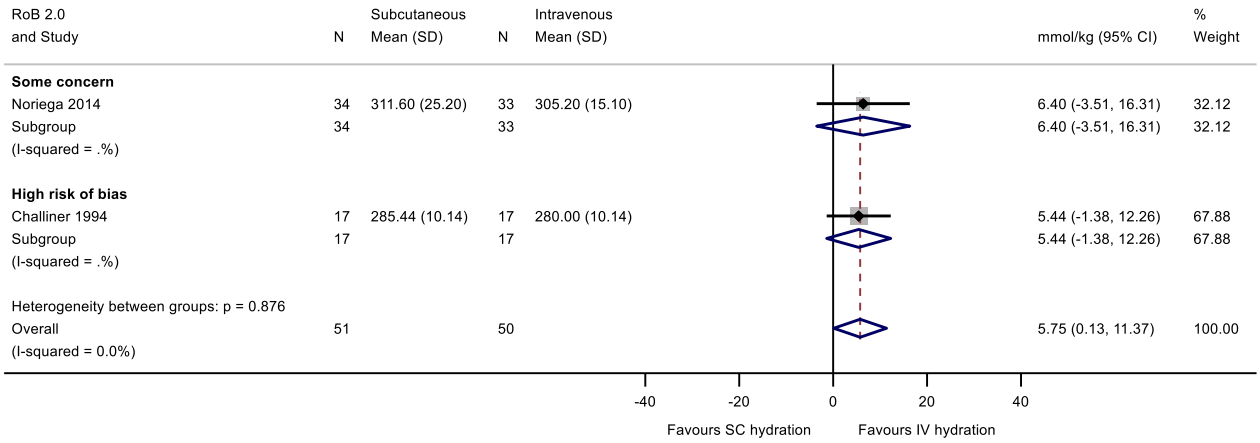
Supplementary Figure S4. Meta-analysis on all the different types of adverse effects comparing subcutaneous vs intravenous hydration



[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:

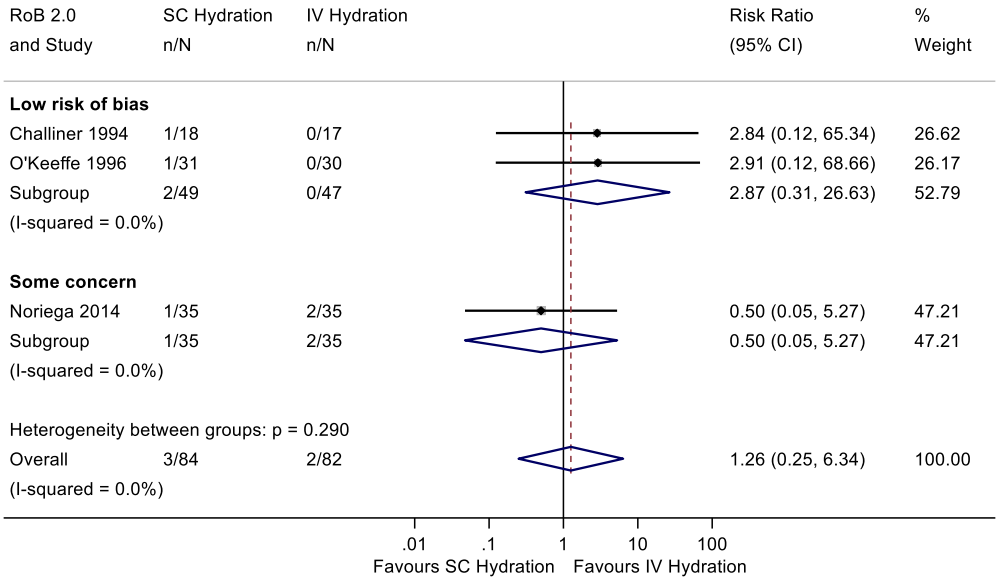
Some concern	z =	1.265	p = 0.206
High risk of bias	z =	1.563	p = 0.118
Overall	z =	2.005	p = 0.045

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:

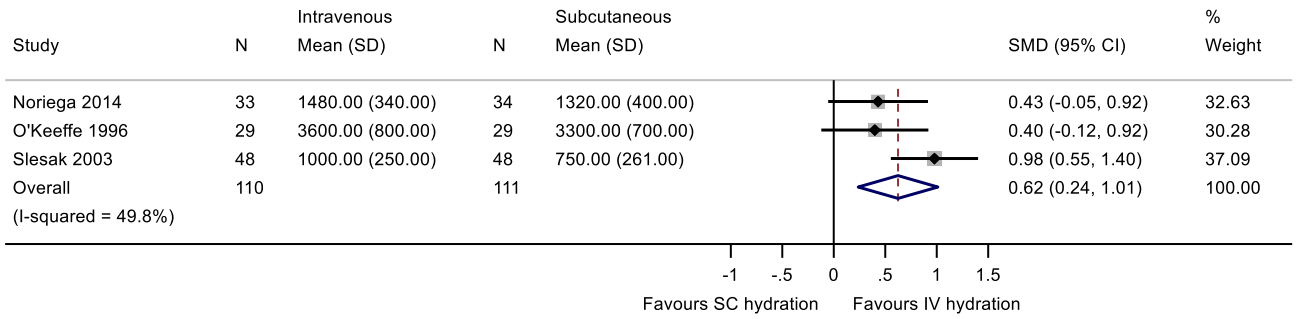
Low risk of bias	z = 0.929	p = 0.353
Some concern	z = -0.577	p = 0.564
Overall	z = 0.279	p = 0.780

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.



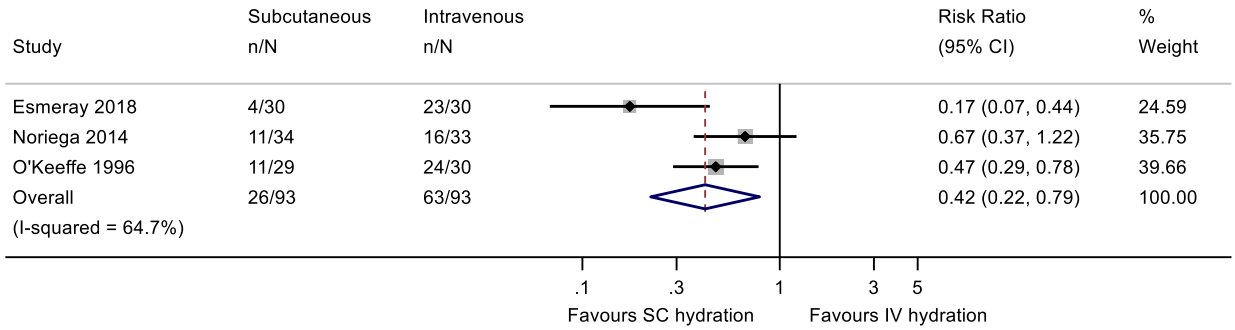
Test of overall effect = 0: z = 3.163 p = 0.002

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.



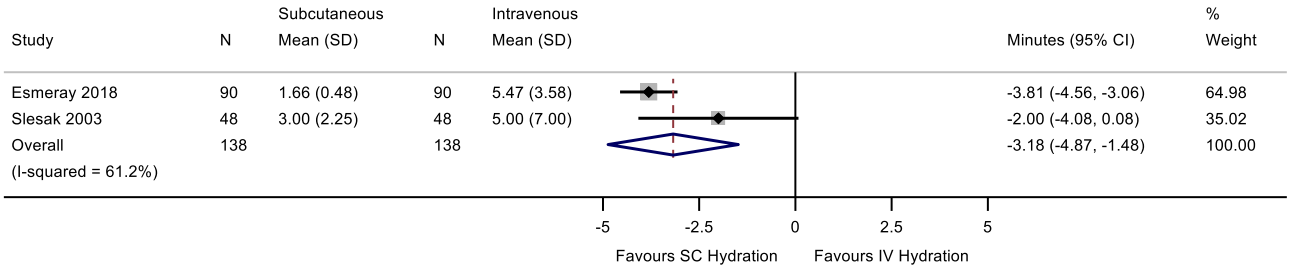
Test of overall effect = 1: z = -2.689 p = 0.007

Heterogeneity Measures

	Value	df	p-value
Mantel-Haenszel Q	6.03	2	0.049
I^2 (%)	64.7%		
Modified H^2	1.831		
tau^2	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.

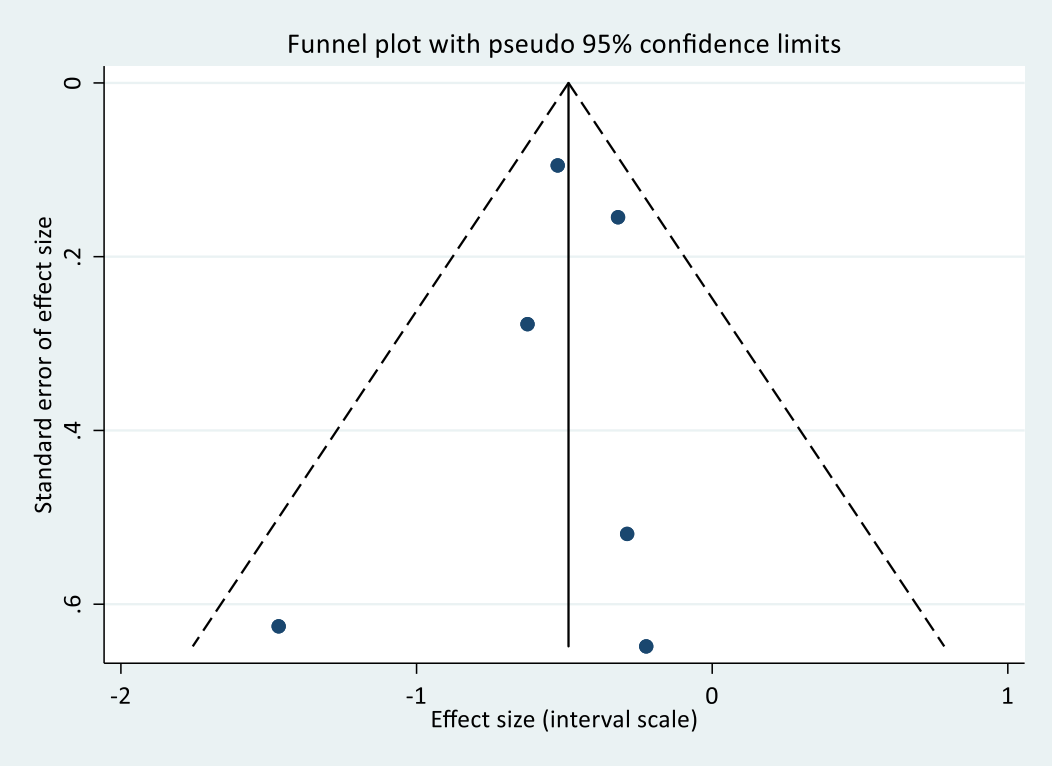


Test of overall effect = 0: z = -3.678 p = 0.00012

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
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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