Vejledning i brug af subkutan væskebehandling hos den ældre patient

Version 1.0

GODKENDT
Faglig godkendelse
11. marts 2023 (Dansk Selskab for Geriatri)
Administrativ godkendelse
11. april 2023 (DSG NBV udvalg)

REVISION
Planlagt: Marts 2026.

INDEKSERING
Dansk selskab for geriatri, væskebehandling, hypodermoclysis

Retningslinjen indeholder, udover de centrale anbefalinger (kapitel 1), en beskrivelse af grundlaget for anbefalingerne – herunder den tilgrundliggende evidens (kapitel 3+4). Anbefalinger mærket A er stærkest, Anbefalinger mærket D er svagest. Yderligere information om styrke- og evidensvurderingen, der er udarbejdet efter "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", findes her: http://www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/oxford-levels-of-evidence-2009_dansk.pdf
Generelle oplysninger om patientpopulationen mv fremgår af kapitel 2, processen omkring retningslinjens tilblivelse fremgår af kapitel 5.

Indholdsfortegnelse

1. Anbefalinger (Quick guide)

Hvilke patienter kan tilbydes subkutan væskebehandling (1)

1. **Ældre patienter, i risiko for eller med let til moderat væskemangel OG insufficient væskeindtag per os, kan tilbydes behandling med subkutan væskebehandling. (B)**

2. **Tilbud om subkutan væskebehandling til umiddelbart døende patienter skal overvejes nøje og er sjældent indiceret. (B)**

3. **Patienter med meget lavt albumin (<20 g/l), subkutant ødem og kutane infektioner ved indstiksstedet bør ikke tilbydes subkutan væskebehandling. (C)**

I hvilke rammer kan subkutan væskebehandling tilbydes (2)

4. **Subkutan væskebehandling kan bruge både i hospitalsregi, på aflastningspladser, på plejehjem og i patientens eget hjem. (B)**

Hvilket kateter bør anlægges og hvor på kroppen (3)

5. **Det subkutane kateter kan placeres i maveskind, lår eller ryg (oven over skulderblad). (C)**

6. **Ved subkutan væskebehandling kan der anvendes et plastikkateter af størrelsen G20-G22. (C)**

Hvor længe kan kateteret blive liggende (4)

7. **Et velfungerende subkutant kateter bør efterses dagligt og skal kun skiftes ved tegn til infektion eller gene for patienten. (D)**

Hvilken type og hvor meget væske kan gives subkutant (5)

8. **Isoton NaCl, 5% glukose og Ringer-lactat kan gives subkutant. (B)**

9. **Der kan gives op til 2 l væske subkutant per dag. Hyppigt gives 1 l over 8-10 timer, men kan også gives som bolus (kamelpukkelmetoden). (B)**

Hvilke bivirkninger kan der opstå ved subkutan væskebehandling (6)

10. **Alvorlige bivirkninger ved subkutan væskebehandling er meget sjældne, men der er beskrevet tilfælde med infektion ved indstiksstedet. (B)**

11. **Der ses ofte et lokalt ødem under infusionen, som forsvinder kort (<2 timer) efter at infusion er slut. Dette vurderes ikke som en bivirkning. (B)**

12. **Milde bivirkninger ses med en incidens på 9 per 100 infusioner og er oftest hæmatom og let smerte ved indstiksstedet. (A)**

Hvad er den kliniske effekt af subkutan væskebehandling (7)

13. **Subkutan væskebehandling har tilfredsstillende effekt på hydreringsgrad ved mild væskemangel og ved patienter i risiko for væskemangel. (B)**

14. **Risikoen for delir er mindre ved subkutan end ved intravenøs væskebehandling. (B)**

Hvilke fordele er der ved subkutan væskebehandling fremfor intravenøs væskebehandling (8)

15. **Det er hurtigere/nemmere at anlægge subkutan end intravenøs adgang. (A)**

16. **Der er færre gener ved anlæggelse og færre bivirkninger under væskebehandling ved en subkutan end ved en intravenøs adgang. (A)**

17. ***Æ*ldre patienter med et behov for parenteral væskebehandling på under 1,5 liter per dag indgivet jævnt i løbet af dagen, og som ikke allerede har en intravenøs adgang eller indikation herfor, kan med fordel behandles med subkutan væskebehandling. (A)**

2. Introduktion

Sufficient hydrering er vigtigt ved behandling af den ældre patient. Korrekt væskebalance er nødvendig for opretholdelse af mange af kroppens vigtige funktioner. Ældre er i øget risiko for væskemangle og dehydrering pga. hyppig forekomst af nedsat tørstfølelse, nedsat evne til at koncentrere urin, nedsat mobilitet, komorbiditeter og medicinsk behandling.[1,2]

Både i primær- og sekundærsektor er dehydrering hos ældre en relativt ofte forekommende tilstand. I en opgørelse fra Italien var 52% af akutte medicinske patienter over 65 år dehydrerede eller havde forestående dehydrering uafhængig af indlægglsesårsag.[3] Ydermere beskrev en rapport fra Sundhedsministeriet fra 2015, at dehydrering var den primære diagnose ved 10,8 % af indlæggelser blandt de 65+-årige og 15,3% blandt de 85+-årige.[4] Tal fra Sundhedsdatastyrelsen beskriver, at der med diagnosen dehydrering var 52 forbyggelige ophold per 1000 ældre i 2021.[5] Et systematisk review, der inkluderede studier fra hele verden, viste at beboere på plejehjem er dehydrering eller i øget risiko for dehydrering hos op til 1/3 af beboerne.[6] Dehydrering er en potentiel farlig tilstand. Patienter, der indlægges med dehydrering på medicinske modtagelser, har en øget morbiditet og mortalitet.[3,7,8] Seneste anbefalinger fra The European Society for Clinical Nutrition and Metabolism anbefaler ældre at drikke 1,6-2 liter væske dagligt, så længde der ikke er en klinisk tilstand, der tilskriver noget andet. Hvis ikke dette kan indtages oralt anbefales parenteralt tilskud.[2] Subkutan væskebehandling er en kendt metode til parenteral væskebehandling, og nævnes i flere af de danske nationale anbefalinger.[9,10]

Denne retningslinje omhandler kun subkutan væskebehandling. Der henvises til andre vejledninger, hvis der ønskes viden om subkutan medicinering.[9]

Formål

Det overordnede formål med retningslinjen er at understøtte evidensbaseret behandling og indsats af høj og ensartet kvalitet på tværs af Danmark. Endvidere at udbrede kendskab og understøtte anvendelsen ved at udarbejde et vejledende dokument om subkutan væskebehandling.

Patientgruppe

Ældre patienter i både primær- og sekundærsektoren, der vurderes at have et behov for parenteral væske. Retningslinjen gælder ikke ved behov for akut væsketerapi til kredsløbspåvirkede patienter med behov for hurtig genopretning.

Målgruppe for brug af retningslinjen

Denne retningslinje skal primært understøtte det kliniske arbejde og udviklingen af den kliniske kvalitet, hvorfor den primære målgruppe er klinisk arbejdende sundhedsprofessionelle i det danske sundhedsvæsen. Retningslinjen er primært rettet mod uddannet sundhedsfagligt personale i både primær- og sekundærsektoren.

3. Grundlag

Hvilke patienter kan tilbydes subkutan væskebehandling (1)

1. Ældre patienter, i risiko for eller med let til moderat væskemangel OG insufficient væskeindtag per os, kan tilbydes behandling med subkutan væskebehandling. (B)

Guidelines om ernæring til ældre patienter fastslår vigtigheden af at opretholde korrekt hydrering.[2,11] Det understreges også, at korrekt hydrering bør opretholdes ved oral hydrering så længde, det er muligt. Først når oralt væskeindtag er insufficient, bør patienter tilbydes parenteral væskebehandling. Hvornår, det kan anbefales at benytte subkutan i forhold til intravenøs væskebehandling, er beskrevet i anbefaling nummer 8.

Vurdering af hydreringsgraden hos ældre patienter er meget kompleks, herunder også vurdering af risikoen for at udvikle væskemangel. Disse områder ligger uden for formålet af denne kliniske retningslinje. Der henvises til ESPEN guideline on clinical nutrition and hydration in geriatrics.[2]

Arbejdsgruppen bag denne retningslinje er også enige med ESPEN guideline i at parenteral hydrering er medicinsk behandling, og derfor som hovedregel kun bør bruges, hvis der er en realistisk chance for klinisk forbedring, hvor patienten selv kan indtage sufficient væske, eller hvis patienten kan opretholde et acceptabelt funktionsniveau ved vedligeholdelses behandling.[2] Derfor anbefaler vi også, at der altid tages stilling til behandlingsvarighed ved opstart af subkutan væskebehandling, for at sikre at der ikke forsættes med formålsløs medicinsk behandling.

2. Tilbud om subkutan væskebehandling til umiddelbart døende patienter skal overvejes nøje og er sjældent indiceret. (B)

Subkutan væskebehandling er parenteral ernæring, og der bør udvises omtanke i forhold til, hvilke patienter der tilbydes denne behandling. Det er omdiskuteret, om døende patienter skal tilbydes parenteral væskebehandling.[12,13] Hvornår en patient er døende, og om de skal tilbydes parenteral væskebehandling, ligger uden for rammen af denne retningslinje.

3. Patienter med meget lavt albumin (<20 g/l), subkutant ødem og kutane infektioner ved indstiksstedet bør ikke tilbydes subkutan væskebehandling. (C)

Da albumin er den primære osmotiske faktor, der trækker/holder væske inde i karbanen, er der en forventning om, at lavt albumin vil føre til dårlig absorption af subkutant infunderet væske.[14] Der er dog ingen studier, der direkte har undersøgt dette. *Danielsen et al.* (2022b) har undersøgt absorptionen af subkutan infunderet væske hos ældre, syge indlagte patienter. De fandt at albumin havde en effekt på absorptionshastigheden, men kunne ikke bedømme størrelsen af denne effekt. De laveste albumin niveauer i dette studie var 23 g/l (1 patient) og 25 g/l (2 patienter), men der sås ikke klinisk betydende nedsat absorptionshastighed hos disse patienter.[15] Klinisk erfaring anbefaler forsigtighed ved albumin under 25 g/l med regelmæssig observation, og bør nok ikke startes ved albumin under 20 g/l.

Ingen randomiserede kontrollerede forsøg (RCT'er) på området har haft lav albumin som direkte eksklusionskriterie, men de fleste beskriver svært kutant ødem som eksklusionskriterie.[16]

I hvilke rammer kan subkutan væskebehandling tilbydes (2)

4. Subkutan væskebehandling kan bruge både i hospitalsregi, på aflastningspladser, på plejehjem og i patientens eget hjem. (B)

Litteratur- og evidensgennemgang

Der er identificeret 8 RCT'er om subkutan væskebehandling i hospitalsregi.[17–24] Effekten af subkutan væskebehandling og risikoen for bivirkninger er beskrevet i hhv. anbefaling nummer 7 og anbefaling nummer 6.

Der findes flere studier, der beskriver brugen af subkutan væskebehandling på "long term care facilities", der kan oversættes til plejehjem/aflastnings- og genoptræningspladser. *Dasgupta et al.* (2000) inkluderede geriatriske patienter med en gennemsnitlig alder på 83 ± 11 år, hvoraf 67% havde en demens diagnose og 18% havde adfærdsforstyrrelser. I alt har studiet data fra 807 infusioner. Subkutan væskebehandling var veltolereret og havde få bivirkninger.[25] Tilsvarende studier kommer til samme konklusion.[26–30]

Subkutan væskebehandling er også undersøgt ved behandling i patienters eget hjem, men studierne er kun udført på palliative patienter og ikke den ældre patient. Det vurderes, at resultaterne fra disse studier i et vist omfang kan anvendes hos ældre patienter generelt. Gennemsnitsalderen for inkluderede patienter i hjemmebehandlingsstudierne er hos de fleste 70-80 år. Der beskrives en metode, hvor en sygeplejerske anlægger det subkutane kateter og at det efterfølgende er pårørende (fx ægtefælle eller barn), der står for at opsætte/ nedtage væsken samt for at kontrollere for bivirkninger.[31–35] Det bedst beskrevne er *Rodrìguez-Campos et al.* (2022). De beskriver et retrospektivt kohortestudie om subkutan væskebehandling i hjemmet varetaget af både pårørende og sygeplejerske. I alt 189 palliative patienter (gennemsnitlig alder på 72 ± 18 år) har modtaget subkutan væskebehandling i hjemmet. I 80% af tilfældene var det administreret af pårørende. Sygeplejerske anlagde kateteret, men derefter stod pårørende for opsætning af væske og observation. De beskriver ingen forskel i behov for kateterskift i forhold til, om det er sygeplejerske eller pårørende, der står for administrationen (p=0,16).[36] Yderligere tre studier har reporteret pårørendes oplevelse af behandling. *Torsheim et al.* (1999) rapporterer, at 8 af 9 pårørende var tilfredse med behandlingen.[34] *Grez et al.* (2020) beskriver, at 51 af 52 pårørende fandt det "nemt" eller "meget nemt" at administrere subkutan væskebehandling.[33] Og *Vidal et al.* (2016) beskriver, at alle pårørende rapporterede "no overall stress" og 18 af 19 pårørende rapporterede ingen problemer.[35]

Rationale

Der er tilfredsstillende beskrivelser af brugen af subkutan væskebehandling både i hospitalsregi, på plejehjem ("long-term care facilities") og i patienters eget hjem. Generelt er der ikke flere komplikationer, når subkutan væskebehandling flyttes ud af hospitalet. Der er dog ikke lavet opgørelser, der direkte sammenligner incidensen af komplikationer. Flere studier beskriver, at pårørende efter oplæring kan varetage både opsætning af væske og kontrol med infusionen i eget hjem. Dog skal det nævnes, at ægtefællen, når der er tale om geriatriske patienter, kan have et lavere funktionsniveau end pårørende i de beskrevne studier, hvilket naturligvis skal tages med i vurderingen af den samlede situation.

Hvilket kateter bør anlægges og hvor på kroppen (3)

5. Det subkutane kateter kan placeres i maveskind, lår eller ryg (oven over skulderblad). (C)

Litteratur og evidensgennemgang

Ingen studier sammenligner direkte placering af det subkutane kateter, men *Lamandé et al.* (2004) lavede et prospektivt kohortestudie, hvor de ikke fandt nogen sikker forskel på bivirkningsfrekvens i forhold til kateter placering, dog med en tendens til øget forekomst af hæmatom, hvis katetret anlægges på ryggen.[27]

Otte RCT'er (7 inkluderer geriatriske patienter og 1 inkluderer palliative patienter) har beskrevet kateterplacering: maveskind (n=8), lår (n=4), bryst (n=4), ryg/over skulderblad (n=4). Der er ikke beskrevet hverken negative eller positive erfaringer med de forskellige placeringer.[17–24]

Rationale

Samlet set er der ingen sikker evidens for, hvor kateteret med fordel kan placeres. Baseret på *Lamandé et al.* (2004), klinisk erfaring og kommentarer fra publicerede studier, anbefales kateteret placeret på maveskind, lår eller ryg over skulderblad.[37] Brugen af kateter anlagt i overarmen kan ikke anbefales, da dette ikke er beskrevet i litteraturen. Placering kan afhænge af den kliniske situation, hvor delirøse patienter kan distraheres af slanger og derfor muligvis vil have glæde af placering på ryggen.

6. Ved subkutan væskebehandling kan der anvendes et plastikkateter af størrelsen G20-G22. (C)

Litteratur og evidensgennemgang

Størrelse

Ingen studier foretager direkte sammenligner af størrelsen af de anlagte katetre, men de fleste studier (både RCT'er og kohortestudier) anvender G20-G22,[17,18,36,38–40,19–24,30,32] og de studier, der har en god rapportering af bivirkninger og gener, har ligeledes brugt G20-G22. Enkelte studier rapporterer brug af kateter ned til G19 og op til G25. Ifølge klinisk erfaring kan der med forsigtighed gives subkutan væske gennem små katetre (G25-G27), dog anbefales infusionshastigheden at være langsom, f.eks. 500 ml over 12 timer. Dette er ikke beskrevet i litteraturen.

Type af kateter

I en oversigtsartikel, der sammenligner plastikkatetre med metalkatetre til subkutan medicinering hos palliative patienter, anbefales at bruge plastikkatetre, der anlægges ved hjælp af en metalstilet, som det kendes fra intravenøse adgange.[41]

Hvor længe kan kateteret blive liggende (4)

7. Et velfungerende subkutant kateter bør efterses dagligt og skal kun skiftes ved tegn til infektion eller gene for patienten. (D)

Litteratur og evidensgennemgang

Der er meget lidt litteratur, der beskriver, hvor længe et subkutant kateter, der bruges til væskebehandling, kan ligge. *Rodrìguez-Campos et al.* (2022) anvender i deres retrospektive kohortestudie, der inkluderer 189 hjemmeinfusioner med subkutan væskebehandling, fast kateterskift efter 20 dage eller før hvis der opstod problemer i form af bivirkninger eller hvis kateteret ikke længere virkede. I studiet var median "kateteroverlevelse" 16 dage, og kun 19% af patienter havde behov for at få skiftet kateteret før tid. Dog var der et ukendt antal, der havde en kortere behandlingsvarighed end 20 dage.[36] *Yap et al.* (2001) fandt i deres retrospektive kohorte studie at i 18 ud af 25 tilfælde, hvor patienter udviklede rødme eller autoseponerede, havde kateteret være indsat i mere end 3 dage.[40]

Rationale

I publikationen "Nationale infektionshygiejniske retningslinjer for brug af intravaskulære katetre" beskrives det at subkutane katetre skal skiftes hver 3 til 5 dag. Det beskrives dog ikke tydeligt, om der er tale om subkutan adgang til medicin eller kun væske. Det fremgår ikke, hvad denne anbefaling er baseret på. Af samme vejledning fremgår det at : "Et velfungerende perifert venekateter med frit indløb og uden tegn på infektion skal således ikke skiftes."[10]

På baggrund af *Rodrìguez-Campos et al.* (2022) anbefales samme overvejelse om skift af subkutane katetre til væskebehandling, som for skift af perifere venekatetre, dvs. at det skal skiftes efter klinisk skøn. De bør dagligt efterses, men så længe der ikke opstår komplikationer, er der ikke indikation for at skifte kateteret. Det skal dog fremhæves at evidensniveauet bag denne anbefaling er begrænset.

Den sterile transparente semipermeable forbinding, der lægges oven på kateteret, bør skiftes minimum hver 7. dag.[10]

Hvilken type og hvor meget væske kan gives subkutant (5)

8. Isoton NaCl, 5% glukose og Ringer-lactat kan gives subkutant. (B)

Litteratur- og evidensgennemgang

Lemandé et al. (2004) har lavet et veludført (vurderet low risk of bias[16]) prospektivt kohorte studie, der undersøger risikoen for bivirkninger i forhold til forskellige typer af subkutant indgivet væske. De har givet 1142 infusioner af 5% glukose + 4g NaCl/l, 184 infusioner af 0,9 % NaCl, 54 infusioner af 5% glukose + 2g NaCl/l og 49 infusioner af 5% glukose + 4g NaCl/l + 2g KCl/l. De opgør frekvensen af hæmatom, ødem og smerte ved infusionsstedet, og finder ingen forskel i bivirkningsfrekvens.[27]

*Rodrìguez-Campos et al. (*2022) har i et retrospektivt kohortestudie på palliative patienter opgjort, hvor ofte katetrene stoppede med at virke eller havde behov for at blive skiftet, i forhold til hvilken type væske, der blev givet. De fandt ingen forskel mellem isoton NaCl (152 patienter), 5% dextrose (79 patienter), og Ringer laktat (36 patienter).[36]

De fleste studier inkluderet i de to systematiske reviews fra 2020 om subkutan væskebehandling har givet en kombination af natriumklorid og glukose/dextrose, isoton natriumklorid eller ren 5% glukose.[16,42]

Slesak et al. (2003), *Šťastná et al.* (2009) og *Rodrìguez-Campos et al.* (2022) har alle givet balanceret elektrolyt væske (Ringer lactat® eller Plasma-Lyte®).[18,36,39]

Der er generelt en forsigtighed med at tilføje kalium til infusioner grundet bekymring for lokal irritation. *Lamendé et al.* (2004) har beskrevet tilføjelsen af kalium til subkutan væskeinfusion. De gav 49 patienter infusion af 5% glukose + 4g NaCl/l + 2g KCl/l. Det svarer til 27mmol/l kalium. De beskriver ingen overhyppighed af bivirkninger og samlet set en frekvens af lette lokale bivirkninger under 5%.[27]

Martìnes-Requelme et al. (2005) undersøgte brugen af subkutan væske på korttarmspatienter i et prospektivt kohortestudie (vurderet high risk of bias [16]). De tilføjede 2-4 mmol/l magnesium ($MgSO_4$), hvis patienterne manglede dette, hvilket blev gjort til 8 af 10 patienter. De beskrev dette som ukompliceret.[38]

Rationale

Det vurderes at der er sufficient evidens til at anbefale brugen af isoton NaCl, 5% glukose/5% dextrose, kombinationer af NaCl og glukose/dextrose og balancerede elektrolyt sammensætninger (Ringer-lactat og Plasmalyte). Kalium og magnesium kan tilsættes til subkutane infusioner, men der anbefales lav infusionshastighed og ekstra hyppig observation af hudområdet omkring kateteret.

9. Der kan gives op til 2 l væske subkutant per dag. Hyppigt gives 1 l over 8-10 timer, men kan også gives som bolus (kamelpukkelmetoden). (B)

Litteratur- og evidensgennemgang

Ingen studier sammenligner direkte forskellige indgivne voluminer eller infusionshastigheder. I de fleste studier gives der mellem 750 ml og 1300 ml per døgn med enkelte gange 1500-2000 ml på et døgn. Studier, der giver hyaluronidase (et enzym der øger den subkutane absorption), er ikke medtaget i denne opgørelse, fordi hyaluronidase ikke er indregistreret til brug i Danmark. Ligeledes er der typisk beskrevet en infusionshastighed på 75-125 ml/time.[16,42] Det svarer til 1 liter givet over 8-10 timer.

Danielsen et al. (2022b) lavede et absorptionsstudie på 6 indlagte geriatriske patienter, som fik 235 ml 0,9% NaCl tilføjet en radioaktiv markør i løbet af én time. Absorptionstiden blev målt ved hjælp af en gammadetektor og man fandt en gennemsnitlig peak absorptionshastighed på 127 ml/time og 90% af den indgivne væske var absorberet en time efter infusion var slut. Deres resultater understøtter således ovenstående infusionshastighed.[15]

Slesak et al. (2003) gav subkutan væskebehandling i form af en bolus infusion på 500 ml over 2-6 timer. Bolus infusionen blev gentaget indtil patienten havde modtaget den ordinerede totale volumen, som var mellem 500 og 1500 ml, hyppigst 1000 ml.[18]

Studiet af *Danielsen et al.* (2022b) støtter anvendelsen af bolusmetoden, der også kaldes kamel-pukkel-metode.[15]

Hvilke bivirkninger kan der opstå ved subkutan væskebehandling (6)

10. Alvorlige bivirkninger ved subkutan væskebehandling er meget sjældne, men der er beskrevet tilfælde med infektion ved indstiksstedet. (B)

Litteratur- og evidensgennemgang

Vurdering af bivirkninger ved subkutan væskebehandling var det primære outcome i et systematisk review af *Danielsen et al.* (2020). Her fandt man incidensen af alvorlige bivirkninger i forbindelse med subkutan væskebehandling på 3,5 per 1000 infusioner (95% CI = 1.3 - 5.6 per 1000; antal studier = 8; 2,876 infusioner). Dette estimat er baseret på studier med den laveste risiko for bias. De beskrevne alvorlige bivirkninger var symptomer på hjertesvigt (0,7 per 1000), lungeødem (0,7 per 1000), lokal infektion, der kræver antibiotika (1,0 per 1000) og betydelig hyponatriæmi (1,0 per 1000). Det kan diskuteres, om symptomer på hjertesvigt, lungeødem og betydelig hyponatriæmi er tegn på manglende/forkert indikation for væskebehandling, mere end en bivirkning af behandlingen. Der er ikke belæg for at risikoen for disse bivirkninger er større ved subkutan væskebehandling end ved intravenøs behandling.[16]

Ud over data fra RCT'er og kohortestudier, rapporteres en enkelt case med alvorlig bivirkning i form af cøkum perforation hos en kakektisk 82-årig kvinde i forbindelse med anlæggelse af kateteret.[43] Denne risiko vurderes dog at kunne undgås ved at sikre en subkutis af en vis tykkelse.

11. Der ses ofte et lokalt ødem under infusionen, som forsvinder kort (<2 timer) efter at infusion er slut. Dette vurderes ikke som en bivirkning. (B)

Litteratur- og evidensgennemgang

Der ses ofte et lokalt ødem ved infusion af subkutan væske. *Danielsen et al*. (2020b) fandt i deres absorptionsstudie, at det tog en time efter at infusionen var færdig til at hovedparten af den infunderede væske var absorberet fra det subkutane rum.[15] Fra det systematiske review er den rapporterede incidens af lokalt ødem meget varierende, og den afhænger formentlig af infusionshastighed og indgivet volumen.[16]

Så længe det lokale ødem forsvinder inden for et par timer efter at infusionen er færdigindløbet, vurderes der ikke at være tale om en bivirkning, men en konsekvens af behandling. Der er ikke belæg for, at et mindre lokalt ødem er til gene for patienten. Hvis patienten klager over at "det spænder" ved infusionsstedet, kan infusionshastigheden sænkes. Dette kan beskrives som en bivirkning i form af smerte, og ikke ødem.

12. Milde bivirkninger ses med en incidens på 9 per 100 infusioner og er oftest hæmatom og let smerte ved indstiksstedet. (A)

Litteratur- og evidensgennemgang

Milde bivirkninger er rapporteret i de fleste artikler om subkutan væskebehandling. Dog er der forskel på, definitionen af bivirkning, samt hvorledes og hvilke bivirkninger, der blev observeret for. F.eks. er der ikke enighed om autoseponering er en bivirkning.

Bivirkningsincidensen af milde bivirkninger er af det systematiske review *Danielsen et al.* (2020) samlet set opgjort til 9 per 100 infusioner (95% CI = 8–10; baseret på 2,876 infusioner) med en rapporteret incidens fra

de enkelte studier på mellem 3 og 18 per 100 infusioner. Disse tal inkluderer kun de bedste studier.[25,27,30,34],[17,18,23,24] Hvis man inkluderer alle studier, falder incidensen til 5,3/100 infusioner. De hyppigste bivirkninger er hæmatom ved indstiksstedet og let smerte ved infusionen. Derefter kommer behov for genanlæggelse af kateteret, rødme, lækage, og autoseponering.[16]

To studier, hvor ca. 1/3 af patienterne var i blodfortyndende behandling, har beskrevet risikoen for hæmatom ved subkutan væskebehandling. De beskriver, at der ikke ses en øget risiko for hæmatom, når patienter er i behandling med blodfortyndende behandling. Dog er antallet af hæmatomer lavt.[19,27]

Langt hovedparten af infusioner bag vurderingen af incidens og type af bivirkninger er lavet på geriatriske patienter. Fire studier med angivelse af incidens er lavet på hospitalsindlagte patienter[17,18,23,24], 3 på plejehjem[25,27,30] og 1 ved hjemmebehandling[34]. Der er ikke belæg for, at der er relevant forskel i frekvensen af bivirkninger mellem de forskellige opholdssteder.

Rationale

Overordnet vurderes den samlede incidens og typen af bivirkninger at være relativt godt undersøgt og beskrevet. Grundet de forskellige metoder og definitioner af bivirkninger kan en sikker incidens af forskellige bivirkninger ikke sikkert opgøres.

Hvad er den kliniske effekt af subkutan væskebehandling (7)

13. Subkutan væskebehandling har tilfredsstillende effekt på hydreringsgrad ved mild væskemangel og ved patienter i risiko for væskemangel. (B)

Litteratur- og evidensgennemgang

I det tidligere nævnte absorptionsstudie på indlagte geriatriske patienter af *Danielsen et al.* (2022b) fulgte man med en gammadetektor den indgivne væske hvori der var opblandet en radioaktivt mærkede markør. Studiet viste at væsken "forsvandt" fra abdomen og blev genfundet i blodet, samt at 88% af den indgivne væske var absorberet en time efter at infusionen var færdigindløbet.[15]

Meta-analysen lavet af *Danielsen et al.* (2020) vurderede effekten af væskebehandling ved hjælp af surrogatmarkørerne: effekt på serum osmolaritet (2 studier) og volumen af indgivet væske (3 studier). De fandt, at intravenøs væskebehandling sænkede serum osmolaritet med 5.75 mmol/kg (95% CI 0,13-11,4 mmol/kg) mere end subkutan væskebehandling, og at der blev givet 155 ml (95% CI 60-253 ml) mere med intravenøs væske per dag, når der blev givet 1000 ml intravenøst. De vurderede også kvaliteten af evidensen baseret på GRADE framework. For begge outcomes blev kvaliteten af evidensen vurderet til at være meget lave, hvilket tolkes som at de sande estimater kan være markant forskellige fra de fundne.[16] Den samme konklusion og vurdering af kvaliteten af evidensen er beskrevet i et systematisk review af *Barreto Annes et al*. (2020).[44]

To RCT'er inkluderer en klinisk vurdering af hydreringsgrad, og finder ingen forskel mellem subkutan og intravenøs væskebehandling.[18,20] Hvad vurderingen er baseret på, er dog enten dårlig beskrevet eller tilstrækkelig forskellig til, at det ikke kan indgå i en meta-analyse.

Broadhurst et al. (2020) beskriver i deres umbrella review, at der ikke er forskel mellem intravenøs og subkutan væskebehandling i forhold til "klinisk bedring". Det er vært at vurdere, hvad klinisk bedring dækker over og hvad der ligger bag denne vurdering.[42]

Subkutan væsketerapi er dog kun undersøgt på patienter med mild væskemangel eller i risiko for væskemangel. Patienter der har et mere akut væskebehov f.eks. ved sepsis med hæmodynamisk påvirkning bør ikke behandles med subkutan væsketerapi uafhængigt af volumen der skal gives, da dette ikke er undersøgt, og da der er risiko for at væskebehandlingen gives for langsomt.

Rationale

Der er evidens for, at subkutant indgivet væske absorberes, men at det kan tage op mod 60 minutter. I de tilfælde, hvor det er vigtigt, at patienten får væsken relativt hurtigt, bør der benyttes intravenøs væskebehandling pga. hurtigere effekt. Derudover er der ikke belæg for at subkutan væskebehandling har mindre effekt end intravenøs behandling.

14. Risikoen for delir er mindre ved subkutan end ved intravenøs væskebehandling. (B)

Litteratur- og evidensgennemgang

Effekten på delir af subkutan i forhold til intravenøs væskebehandling er beskrevet både i det systematiske review af *Danielsen et al.* (2020) og i umbrella review'et fra *Broadhurst et al.* (2020).[16,42]

Danielsen et al. (2020) finder i deres meta-analyse, baseret på 3 studier, en relativ risiko på 0,42 (95% CI 0,22-0,79) til fordel for subkutan væske. Kvaliteten af evidens, baseret på GRADE framework, er dog vurderet til "lav", pga. af forskellige måder at vurdere/måle delir samt risk-of-bias i de inkluderede studier.[16] Broadhurst et al. (2020) konkluderer det samme.[42]

Rationale

Baseret på litteraturen er der en reduceret risiko for delir ved behandling med subkutan væske i forhold til med intravenøs væske ved væskemangel/risiko for væskemangel.

Hvilke fordele er der ved subkutan væskebehandling fremfor intravenøs væskebehandling (8)

15. Det er hurtigere/nemmere at anlægge subkutan end intravenøs adgang. (A)

Litteratur- og evidensgennemgang

Meta-analysen af *Danielsen et al.* (2020) viser, at det tager 3,2 minutter (95% CI = 1.5–4.9 minutter) mindre at anlægge en subkutan end en intravenøs adgang.[16] *Danielsen et al.* (2022a) finder også i deres RCT, at det er signifikant hurtigere at anlægge den subkutane adgang.[19] Ligeledes viser data fra et nyligt RCT af *Chanthong et al.* (2022), at der bruges færre nåle, samt at personalet synes, at det er lettere at anlægge subkutane adgange.[22]

Adem et al. (2021) beskriver, at de på 1 time har oplært sundhedspersonale i anlæggelse af subkutan adgang inklusiv oplæring i relevant observation, og at det ikke har givet problemer.[31]

Rationale

Selvom det er nemmere at måle og beskrive, er de minutter, der spares, nok mindre klinisk relevante end personalets præferencer. At sundhedspersonale kan anlægge adgangen efter blot en times oplæring sammenholdt med tidsbesparelsen underbygger, at det er nemt at anlægge subkutane adgange.

16. Der er færre gener ved anlæggelse og færre bivirkninger under væskebehandling ved en subkutan end ved en intravenøs adgang. (A)

Litteratur- og evidensgennemgang

En meta-analyse med efterfølgende GRADE vurdering udført af *Danielsen et al.* (2020) finder en relativ risiko for bivirkninger ved behandling med subkutan i forhold til intravenøs væskebehandling på 0,69 (95% CI 0,53-0,88). Der er således 31% lavere risiko for bivirkninger ved at give en subkutan væskeinfusion i forhold til intravenøs væskeinfusion. Omregnet til absolutte tal giver det en incidens af bivirkninger på 9 per 100 subkutane væskeinfusioner i forhold til 13 per 100 intravenøse væskeinfusioner. De vurderer, at kvaliteten af evidens er moderat, hvilket betyder, at estimatet er godt, men ikke helt præcist.[16]

Chanthong et al. (2022) lavede et RCT, hvis primære outcome var vurdering af smerte ved anlæggelse vurderet på en "pain numeric rating score" fra 0-10. Patienterne vurderede statistisk signifikant mindre smerte ved subkutan end ved intravenøs anlæggelse, med scorer på hhv. 1,9 og 4,2.[22]

Danielsen et al. (2022a) fandt tilsvarende resultat, dog uden at resultatet var statistisk signifikant. De vurderede smerte ved anlæggelse på en VAS fra 0-100 og fandt en score på 7,3 ved subkutan og på 13,0 ved intravenøs anlæggelse.[19]

Rationale

Samlet set er der god evidens fra et systematisk review baseret på RCT'er, der viser at der er færre bivirkninger ved subkutan end ved intranøs væskebehandling. Incidensen af bivirkninger er dog relativ lav ved begge metoder hvorfor den absolutte reduktion er beskeden.

Der er også velundersøgt i RCT'er at der er mindre smerte ved anlæggelse af subkutane adgang end ved anlæggelse af intravenøs adgang.

17. Ældre patienter med et behov for parenteral væskebehandling på under 1,5 liter per dag indgivet jævnt i løbet af dagen, og som ikke allerede har en intravenøs adgang eller indikation herfor, kan med fordel behandles med subkutan væskebehandling. (A)

Rationale

Denne anbefaling er en sammenfatning af de ovenstående anbefalinger.

Hos patienten med et relativt begrænset parenteralt væskebehov (under 1,5-2 liter per dag), er der ikke belæg for at subkutan væskebehandling har klinisk relevant mindre effekt end intravenøs væskebehandling. Dette gælder dog kun ved patienter uden behov for hurtig væskeinfusion. Ved subkutan væskeindgift kan der gives op til 1 l over 8-10 timer. Hvis der er behov for at væsken skal gives hurtigere, bør der vælges en anden metode.

Der er ses færre bivirkninger ved subkutan væskebehandling og mindre risiko for delir end ved intravenøs væskebehandling. Bivirkningsfrekvens er baseret på studier med daglige volumen på under 1,5-2 liter per

dag. Ved behov for større voluminer er evidensen ikke tilstrækkelig til at vurdere effekten eller bivirkningsfrekvens.

Ved kontraindikationer mod subkutan væske i form af lavt albumin (<20 g/l), subkutant ødem eller kutane infektioner ved anlæggelsesstedet, bør en anden metode til parenteral hydrering bruges.

Den subkutane adgang er hurtigere at anlægge og udsætter patienten for færre gener ved anlæggelse end ved intravenøs anlæggelse.

Der er ikke tilstrækkelige fordele ved subkutan væskebehandling til at det skal anlægges, hvis patienten allerede har en intravenøs adgang. Hvis der er indikation for anlæggelse af intravenøs adgang f.eks. ved forventning om fremtid brug må valg af adgang ske ud fra et klinisk skøn.

De fleste almindelige typer af infusionsvæsker kan gives subkutant.

Der bør ved opstart af subkutan væskebehandling tages stilling til behandlingsvarigheden, for at sikre at der ikke forsættes formålsløs medicinsk behandling.

Der er evidens for, at subkutan væskebehandling kan gives af oplært sundhedsfagligt personale alle steder, hvor den ældre patient opholder sig.

4. Referencer

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5. Metode

Litteratursøgning

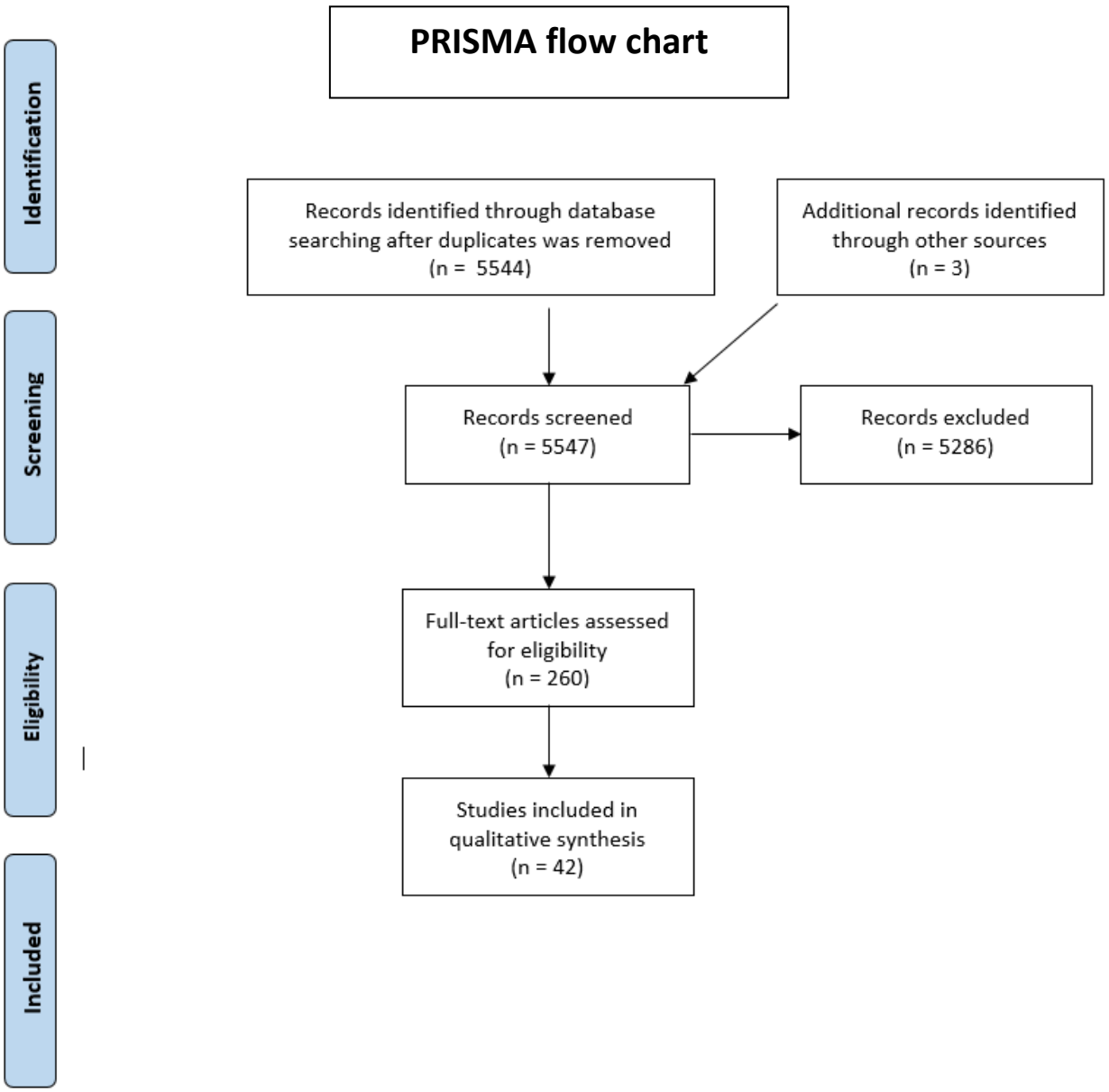
Søgningen er en opdateret søgning fra det systematiske review af Danielsen et al. (2020).[16] Derudover lavede vi også en gennemgang af alle de studier, der blev ekskluderet i full text grundet manglende data på bivirkninger, som var et eksklusionskriterie i det systematiske review. Søgningen er gjort bred for at sikre, at al litteratur med patientdata på subkutan væskebehandling blev fundet. Derudover er fundet de nyeste systematiske reviews på området. Litteratursøgning er foretaget i følgende databaser i september 2022: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials og Web of Science. Søgningen indeholdt følgende termer: Hypodermoclysis, subcutaneous hydration og kombination af synonymer for væskemangel og subkutan infusion. Se bilag 1 for fuld søgestreng for de søgte databaser.
Der er ikke brugt begrænsning på udgivelsestidspunkt, sprog eller alder af patienter i søgningen.

De fundne artikler er screenet i dupleks af Mathias Danielsen og Stig Andersen. Først på titel og abstract. Derefter er alle screenet på fuld tekst. Alle artikler på andre sprog end engelsk og en af de nordiske sprog blev oversat via Google Translate.[45,46] Følgende var in- og eksklusionskriterier:
Inklusionskriterier:

1) Alle type studier der har direkte patient data. Derudover er de nyeste systematiske reviews også relevante
2) Alle typer af artikler. Dvs. både tidsskrift artikler, konference abstract og case reports
3) Der var ingen restriktion på sprog eller publikationsdato
4) Studier skulle dog omhandle ældre patienter (alder over 65 år eller gennemsnitlig alder over 60 år)
5) Studierne skulle inkludere subkutan væskebehandling og have data på dette uden samtidig subkutan medicin indgift

Eksklusionskriterie:

1) Studier, der omhandlede subkutan medicinering, subkutan parenteral ernæring eller relevansen af hyaluronidase.



Litteraturgennemgang

Udvælgelsen af relevante studier ud fra søgning og dataekstraktion blev gjort i duplex af Mathias Danielsen og Stig Andersen. Uoverensstemmelser blev løst ved diskussion. Alle studier, der har primære patient data, blev beskrevet og vurderet om de indeholdte informationer havde betydning for udfærdigelse af anbefalingerne. Ikke alle studier, der indeholder data, er refereret i retningslinjen. Se bilag 2 for et kort data resumé af studierne, der indeholdt data på subkutan væskebehandling.

Formulering af anbefalinger

Det blev via konsensus i hele arbejdsgruppen besluttet, hvilke områder/spørgsmål retningslinjen skulle besvare. Anbefalingerne er skrevet ud fra den fundne litteratur af Mathias Danielsen med sparring fra Stig Andersen.

Herefter blev retningslinjen udsendt til arbejdsgruppen, og over to omgange blev anbefalingerne tilrettet, så arbejdsgruppen er enige om de endelige anbefalinger.

Interessentinvolvering

Den kliniske retningslinje er udviklet uden ekstern støtte.

Der har ikke været direkte patient- eller pårørende-involvering i udarbejdelsen af nærværende kliniske retningslinje.

Høring og godkendelse

Denne retningslinje er forhåndsgodkendt af Bestyrelsen i Dansk Selskab for Geriatri. Herefter er retningslinjen godkendt og vurderet efter vanlige standarder for godkendelse af retningslinjer i DSG.

Retningslinjen er vurderet og godkendt på Dansk Selskab for Geriatris årsmøde 2023.

Retningslinjen har været udsendt til DSG's medlemmer før årsmødet. Alle DSG-medlemmer har haft mulighed for at kommentere retningslinjen til årsmødet eller ved at sende skriftlige kommentarer direkte til arbejdsgruppen.

Anbefalinger, der udløser betydelig merudgift

Anbefalingen vurderes ikke at udløse merudgift.

Behov for yderligere forskning

1) I hvilket omfang subkutan væskebehandling nedsætter risikoen for delir i forhold til behandling med intravenøs væskebehandling er et område med behov for yderligere forskning. Hvis estimatet på knap 60% reduktion er bare nogenlunde korrekt, vil det ændre, hvornår patienterne skal tilbydes subkutan væskebehandling, og potentielt spare både patienter, pårørende, sundhedspersonale og samfund for meget.
2) Den kliniske og samfundsøkonomiske effekt af væskebehandling uden for hospitalsregi er ikke undersøgt i randomiserede undersøgelser. Specielt kunne det være interessant at belyse, om øget tilbud af subkutan væskebehandling på plejehjem og aflastningspladser kan forbygge indlæggelser.
3) Brug af små katetre <G25 er ikke tilstrækkelig undersøgt, men da de ofte bruges til subkutan medicinering, giver det mening at undersøge i hvilket omfang, der kan gives væske igennem dem.
4) Hvor længe et subkutant kateter, der kun bruges til væskeindgift, kan ligge, er ikke tilstrækkelig undersøgt. Der er dog studier, der tyder på at det kan ligge længe uden problemer.

5) Bivirkningsprofil og incidens hos særlig risikogrupper: kakeksi, diabetes og blodfortyndende behandling.

Forfattere og habilitet

- Mathias Brix Danielsen, Geriatri, konst. 1.reservelæge, Geriatrisk afdeling, Aalborg Universitetshospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje
- Lone Winther Lietzen, Geriatri, Afdelingslæge, klinisk lektor, Ældresygdomme, Aarhus Universitetshospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje.
- Karen Andersen-Ranberg, Geriatri, Professor og ledende overlæge, Odense Universitetshospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje
- Lene Holst Pedersen, Geriatri, Afdelingslæge, Ældresygdomme, Aarhus, Universitetshospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje
- Solvejg Henneberg Pedersen, Geriatri & Intern Medicin. Ledende overlæge, Medicin 2, Holbæk sygehus, ingen interessekonflikter ift. anbefalingerne i denne retningslinje
- Martin Schultz, Geriatri, Afdelingslæge, klinisk lektor, Medicinsk Afdeling, Geriatrisk sektion, Herlev og Gentofte Hospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje
- Charlotte Suetta, Geriatri, Professor og Overlæge, Geriatrisk og Palliativ afdeling, Bispebjerg og Frederiksberg Hospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje.
- Stig Andersen, Geriatri, Professor og cheflæge, Aalborg Universitetshospital, ingen interessekonflikter ift. anbefalingerne i denne retningslinje

For detaljerede samarbejdsrelationer henvises til deklaration via Lægemiddelstyrelsens hjemmeside: https://laegemiddelstyrelsen.dk/da/godkendelse/sundhedspersoners-tilknytning-til-virksomheder/lister-over-tilknytning-til-virksomheder/apotekere,-laeger,-sygeplejersker-og-tandlaeger

Samlet vurdering af habilitet for forfattergruppen:
Da ingen forfatterne har interessekonflikter, vurderes der ikke at være habilitetsproblemer.

Version af retningslinjeskabelon

Retningslinjen er udarbejdet i version 9.2.1 af skabelonen fra Danske Multidisciplinære Cancer Grupper (DMCG.dk).

6. Monitorering

Der er ikke planlagt en monitorering om brugen af anbefalingerne. Der vil hver tredje år blive fortaget en gennem af ny litteratur på området, nedsætte en arbejdsgruppe og opdaterer anbefalingen hvor relevant.

7. Bilag

Bilag 1 – Søgestrategi

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

Bilag 2 - Resumé af studierne om subkutan væskebehandling

Study characteristics of relevant studies on subcutaneous hydration

2.1 Systematick reviews

BarretoAnnes 2020[44]

Methods	**Publication type:** Journal article **Study design:** Systematic review **Country of study:** NA **Language of publication:** English **Year of study:** NA **Source of funding:** No information **Aim of study:** Compare SC and IV on the effect in reversing dehydration **Aim of intervention:** NA **Sample size calculation:** NA
Participants	**Recruitment:** No data **Inclusion/exclusion criteria:** RCT/excl. all other study design **Type of patient:** Moderate to severe dehydration **Age:** 60+ years **Setting:** Geriatric Hospitals in Europe **Sex:** No data **Number of participants:** 197
Interventions	**Intervention:** Subcutaneous hydration **Comparator:** Intravenous hydration **Fluid type infused:** Isotonic Saline, Saline-dextrose, Glucose, Glucose-saline **Duration of intervention:** 6-48 hours **Number of infusions:** No data **Infusion site duration:** No data **Use of hyaluronidase:** Not described
Outcomes	**Adverse effects** They evaluated the adverse effects separately. They evaluated Cellulitis, edema, phlebitis, erythema, and hyponatremia. Only in the risk of phlebitis was there a significant difference. **Serum osmolality** They found in their meta-analysis that SC was inferior to IV in lowering osmolarity in the first 24 hours, and non significant inferior at 48 hours. Both with low quality of evidence (GRADE)
Notes	

Broadhurst 2020[42]

Methods	**Publication type:** Journal article **Study design:** Umbrella review **Country of study:** NA **Language of publication:** English **Year of study:** NA **Source of funding:** Partial grant from BD **Aim of study:** Safety, acceptability, effectiveness, efficiency of subcutaneous hydration; mechanisms of delivery: 1. Clinical response; 2. Adverse events (abscess, erythema, bruising, electrolyte imbalance, oedema, infection, pain, fluid overload, vascular collapse, route failure); 3. Survival; 4. Acceptability; 5. Efficiency.

Aim of intervention: Treat mild and moderate dehydration.
Sample size calculation: NA

Participants

Recruitment: No patient data. Studies in English identified in a systematic search June 2020 of databases: Embase, PubMed, CINAHL, Cochrane Database of Systematic Reviews, Joanna Briggs Institute of Systematic Reviews, Database of Abstracts of Reviews of Effects.
Inclusion/exclusion criteria: Participants of any age, gender, diagnosis, geography, and healthcare setting. Studies were included if they were published 1990 or later; had clear objectives; explicit methods; assessment of validity; systematic presentation / exclusion: non-English
Type of patient: Pt with mild to moderate dehydration
Age: No restriction
Setting: Hospital, palliative care, hospice, long term care.
Sex: No restriction.
Number of participants: Patients uncertain (n=164 in RCTs; total numbers mentioned add up to >1000).
Studies: 26 systematic reviews, of which 9 focused on fluids, 3 on fluids and medication, 14 on medication.

Interventions

Intervention: Subcutaneous hydration
Comparator: Intravenous hydration
Fluid type infused: Typical sodium chloride, saline-dextrose solutions
Duration of intervention: Average of 5 days for the old. Change of site every 2-3 days
Number of infusions: No data. For older people average rate of 50 (30-80) mL/h, daily volume (mean; range 1340; 698-1708 mL)
Infusion site duration: Abdominal wall, upper chest (most common)
Use of hyaluronidase: Some, not included in assessment here

Outcomes

All outcomes are summarized in table 4 including a grade evaluation.
See table 4 in paper. We cannot copy it here due to copyright.

Adverse effects

Effectiveness

Acceptability

Infusion rate

Volumen

Duration

SC site

Notes

Danielsen 2020[16]

Methods

Publication type: Systematic review
Study design: Systematic review
Country of study: NA
Language of publication: English
Year of study: NA
Source of funding: No external funding

	Aim of study: To compare the risk of adverse effects between SC and IV hydration in older patients and to estimate the incidence and profile of adverse effects. The additional aims were to compare the clinical effects of SC and IV hydration. **Aim of intervention:** NA **Sample size calculation:** NA
Participants	**Recruitment:** Studies: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, and cross-referenced of included studies. **Inclusion/exclusion criteria:** All studies published prior to November 2019 were included. No restriction on language, publication date, setting. Age: >65 years or mean >60 years. Search terms: hypodermoclysis, subcutaneous, rehydration, fluid therapy, fluid administration, infusions, solutions, dehydration, hypovolemia, fluid resuscitation. **Type of patient:** Study: 7 RCTs, 1 case-control, 11 prospective cross-sectional, 6 retrospective cross-sectional, 4 case reports. **Age:** Median 82 years, range 61-85. **Setting:** No restrictions (14 hospital, 6 short-/long-term care facilities, 8 both). **Sex:** No restrictions. **Number of participants:** 29 studies. RCT: 320 patients in 6 of 7.
Interventions	**Intervention:** Subcutaneous hydration. **Comparator:** IV or no comparator. **Fluid type infused:** N/A **Duration of intervention:** N/A **Number of infusions:** 10,970 in total. RCT: 1483 infusions. Observational: 9,487 infusions. **Infusion site duration:** Abdomen, infraclavicular, scapular, abdomen, thigh. **Use of hyaluronidase:** No.
Outcomes	**Table 2. GRADE Summary of Findings: Subcutaneous Hydration** See table 2 in paper. We cannot bring it here due to copyright.
Notes	

2.2 Randomized studies

Challiner 1994[23]

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 liters 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 liter 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.

Chanthong 2022[22]

Methods

Publication type: Journal article
Study design: RCT
Country of study: Thailand
Language of publication: English
Year of study: No data
Source of funding: Jubilee Medical Center

	Aim of study: Pain experience of SC vs IV insertion **Aim of intervention:** Hydration **Sample size calculation:** On pain of insertion. 24 patients needed
Participants	**Recruitment:** At a palliative care unit **Inclusion/exclusion criteria:** 18+ who require hydration and admitted to a palliative care unit, Excl.: skin infection, edema, heart failure, volume overload, chronic kidney disease, allergy to fluid, refusal of consent. **Type of patient:** Palliative patients **Age:** Mean: SC: 73.1-+15.9 IV: 74.5-+11.8 **Setting:** Palliative care unit **Sex:** male/female; SC: 4/8, IV: 6/8 **Number of participants:** 26
Interventions	**Intervention:** SC hydration, 22- and 24-gauge catheter in upper chest, suprascapular og abdomen. Max infusion rate was 120 ml/hour **Comparator:** IV hydration with 22 or 24 gauge. **Fluid type infused:** Doctor's choice, no information on fluid infused **Duration of intervention:** No information, but properly only one insertion per patient was done. **Number of infusions:** Duration * number = SC= (2.3*12) = 27.6 infusions; IV = 2.6*14= 36.4 infusions, sc/iv infusion rates 20-60 / 20-80 mL/h; volume 2300/2997 mL **Infusion site duration:** Duration of catheter placement, SC: 2.3+-0.9, IV:2.6+-0.9. Catheters changed after 72 hours. **Use of hyaluronidase:** No information
Outcomes	**<u>Adverse effects</u>** **Outcome definition:** "checked for any adverse reaction daily", phlebitis, erythema, leakage **How was the outcome assessed:** Nursing staff **Result:** Complication was seen in 25% of SC group, and 42,6% of IV group **<u>Ease of insertion of catheter</u>** **Outcome definition:** Clearly defined **Unit of measurement:** 1-6 Likert scale **How was the outcome assessed:** Nurses was asked **Result:** Score SC: 1.7-+0,8 IV: 4.1-+1.5 **<u>Volume infused</u>** **Outcome definition:** Total volume of infused fluid is reported. **Unit of measurement:** ml per day*** **Result:** SC 2300ml/2,3days= 1000 ml per day, IV: 2997 ml/2,6 days = 1153 ml per day
Notes	

Danielsen 2022a[19]

Methods	**Publication type:** Journal article **Study design:** RCT **Country of study:** Denmark **Language of publication:** English **Year of study:** 2020-2021 **Source of funding:** No external funding **Aim of study:** Compare IV and SC hydration on risk of adverse effects **Aim of intervention:** Hydration **Sample size calculation:** Based on studies with <48h observation: 67 in each group
Participants	**Recruitment:** Hospital, hip fracture, short-term care

	Inclusion/exclusion criteria: age 65 years or older, a prescription of 1–2 litres of parenteral fluid over the next 24 hours (mild dehydration or at risk of dehydration), and admission to either acute assessment unit, an orthopaedic ward with a hip fracture, or admission to a short-term care facility. Exclusion criteria were: Severe dehydration (expected to need more than 2 L of parenteral fluid over the next 24 hours), fluid restriction, unable to give informed consent, severe general oedema, or planned discharge from the hospital or care facility within the next 24 hours. **Type of patient:** Geriatric patient, from Acute assessment unit, short-term care facility, or orthopaedic ward. **Age:** SC: 79 +- 7.3, IV: 83+- 6.9 **Setting:** Hospital and short-term care **Sex:** 64% female **Number of participants:** 51 in total
Interventions	**Intervention:** 1 l of NaCl, 22g butterfly needle, placed on the abdomen. **Comparator:** IV 22 g catheter **Fluid type infused:** NaCl **Duration of intervention:** 24 hours **Number of infusions:** 51 infusions **Infusion site duration:** 24 hours **Use of hyaluronidase:** No use
Outcomes	AE, sc/iv: 28%/43%; Inferiority: no (p=0.012) Superiority: RR 0.66 (0.29-1.49) (p=0.36 for first; p=0.19 for all AE)
	See table 2 in paper. We cannot copy it here due to copiright.
Notes	

Delamaire 1992[47]

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[21]

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."), inserted on the abdomen. **Comparator:** IV hydration (No further information described in the paper.) **Fluid type infused:** NaCl **Duration of intervention:** 3 SC infusions and 3 IV infusions. 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 oedema, 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[20]

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, no described exclusion criteria
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."). Up to 1,5 liters per day. Catheter was changed every 48 hours or when local complications occurred.
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

Adverse effects
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[24]

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.

Volume
SC: 1320 +- 400; IV: 1480 +-340 per day

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[17]

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 Examination 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 administered through and 18-20-gauge cannula in the forearm veins")

	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 behaviour (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[18]

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 oedema, 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. No information on why the catheters were changed. **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 oedema, large erythema, Cellulitis, Large phlebitis, severe pain, Leakage/paravasal, Minor erythema, Minor oedema, 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.

2.3 Non-randomized studies

Adem 2021[31]

Methods	**Publication type:** Journal article **Study design:** Prospective observational **Country of study:** Saudi-Arabia **Language of publication:** English **Year of study:** 2015-2016 **Source of funding:** No external funding **Aim of study:** To assess the utility, safety, and effectiveness of SC hydration at home on palliative patients

	Aim of intervention: Hydration **Sample size calculation:** No information
Participants	**Recruitment:** Patients discharged from oncology centre for home health care **Inclusion/exclusion criteria:** Adults with advance cancer and dehydration in need of parenteral hydration **Type of patient:** Palliative patient **Age:** 72 +- 10.8 **Setting:** Home care **Sex:** Male: 7, Female: 2 **Number of participants:** 9
Interventions	**Intervention:** SC hydration, no information on catheter size, the cannula was changed every 72-96 hours. **Comparator:** None **Fluid type infused:** Sodium chloride (55.5%), Dextrose-Sodium Chloride (44.4%) **Duration of intervention:** Mean 3.2 days +- 1.1 day **Number of infusions:** 25 **Infusion site duration:** No information **Use of hyaluronidase:** No use
Outcomes	**Adverse effects** **Outcome definition:** No information **How was the outcome assessed:** Pt was monitored by caregiver, reported by phone calls. Symptom assessment: Edmonton symptom Assessment System revised Scale. Caregiver satisfaction: 8/9 were satisfied, one was undecided. "One (3.6%) patient developed redness" … "of the skin which later subsided with no intervention." Symptom relief "patients' perception of nausea, loss of appetite, and energy" "differed significantly from baseline measures" From Discussion: "Infusion of an average of 833 mL over 3-4 days can … relieve some of their symptoms with minimal side effects and local toxicity"
Notes	

Agar 2022[48]

Methods	**Publication type:** Journal article **Study design:** Prospective, multisite, cohort study, using registry-format **Country of study:** Australia, Germany, UK, Canada, Malaysia **Language of publication:** English **Year of study:** 2015-2018 **Source of funding:** No external funding **Aim of study:** Evaluate net clinical effect, (harms and benefits) **Aim of intervention:** Hydration **Sample size calculation:** None; sample size was pragmatic estimate of 100
Participants	**Recruitment:** No information **Inclusion/exclusion criteria:** Patients where SC hydration was going to be commenced. **Type of patient:** Palliative care patients, hospitalized **Age:** 71 (IQR 57-83) **Setting:** Palliative care centres **Sex:** 57% male

	Number of participants: 99 included; benefits and harms data on 88
Interventions	**Intervention:** SC hydration, no information on catheter type and size **Comparator:** None **Fluid type infused:** Normal saline 92%, dextrose (2%), both (3%), other (3%) **Duration of intervention:** No information **Number of infusions:** Mean volume was 925 ml +-459 **Infusion site duration:** 2,9 -+2,9 days **Use of hyaluronidase:** No information **Site of infusion:** Abdomen 39,4%, Chest 6,1%, Arm 27,3%, leg 18,2%, other 3%
Outcomes	**Adverse effects** **Outcome definition:** a priori, oedema, urinary frequency, or retention, ascites, pulmonary oedema, infusion site reaction, capillary leak syndrome, dyspnoea **How was the outcome assessed:** 24-hour post infusion of SC fluid **Results:** 57/93 reported no harm. The most common harm was oedema **Effect of treatment** 33% had benefits in the primary target symptom, and 56,8 had benefits in any target system.
Notes	

Arinzon 2004[30]

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, g 21 in thighs **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[49]

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[50]

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, g 25 in the abdomen or chest (obs. hyaluronidase) **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[51]

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[52]

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	**Adverse effects** **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[53]

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 on the abdomen, no information on cathere size, mean volume over 24 hours: 1300 ml +- 650 ml, contiuous infusion **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.

Coelho 2020[32]

Methods	**Publication type:** Journal article **Study design:** Retrospective observational **Country of study:** Brazil **Language of publication:** English **Year of study:** 2016-2017 **Source of funding:** No external funding **Aim of study:** Patient symptom management by SC hydration, and place of death **Aim of intervention:** Hydration and medication **Sample size calculation:** No information
Participants	**Recruitment:** All patient in the home-based palliative care program **Inclusion/exclusion criteria:** cancer patients in a single home care palliative program (Belo Horizonte, Brazil) **Type of patient:** Palliative patients **Age:**73+-15 **Setting:** Home setting **Sex:** 58.6% female **Number of participants:** 333 HDC in 258 (255)

Interventions	**Intervention:** SC needle gauge 22-24, infusion rates were 1500 ml/day. Reported site of insertion was: Thorax 102 (39.5%), Abdomen 73 (28.3%), Other 3 (1.2%), Missing 110 (42.6%) **Comparator:** None **Fluid type infused:** No information **Duration of intervention:** 11.4 +- 23.9 days **Number of infusions:** 243 patients received hydration. Total number of infusions 243*11.4 days = 2770 infusion* **Infusion site duration:** infusion site changed every 24-48 hours or after 1500-2000 ml had been infused. **Use of hyaluronidase:** No information
Outcomes	**Adverse effects** **Outcome definition:** No information **How was the outcome assessed:** No information Results: Swelling: 7 (3%), Abscess: 5 (2.1%), Erythema: 4 (1.7%), Other: 7 (3%) Used without complications.
Notes	*Assuming one infusion per day. There is no information to support if this is the case.

Danielsen 2022b[15]

Methods	**Publication type:** Journal article **Study design:** Clinial study **Country of study:** Denmark **Language of publication:** English **Year of study:** 2020 **Source of funding:** No external funding **Aim of study:** To estimate the time from infusion to availability in the circulation **Aim of intervention:** Fluid therapy **Sample size calculation:** 6 participants
Participants	**Recruitment:** Convenience sample from a geriatric ward **Inclusion/exclusion criteria:** +75 years. No contraindikations for SC hydration **Type of patient:** Geriatric patients **Age:** 81 +- 2.1 years **Setting:** Hospital **Sex:** 3 male, 3 female **Number of participants:** 6
Interventions	**Intervention:** 250 ml fluid infused over 1 hour, 22 G butterfly needle **Comparator:** NA **Fluid type infused:** 0.9% NaCl **Duration of intervention:** NA **Number of infusions:** 1 **Infusion site duration:** NA **Use of hyaluronidase:** No use
Outcomes	**Results:** Acceptable absorption rates with 88% absorbed one hour after the end of the infusion.
Notes	

Dasgupta 2000[25]

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, no information on size, or placement. Infusion rate was 20-75 ml/hour. **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	**<u>Adverse effects</u>** **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[54]

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.

Grez 2017[33]

Methods	**Publication type:** Abstract **Study design:** Prospective observational **Country of study:** No information **Language of publication:** English **Year of study:** No information **Source of funding:** No information **Aim of study:** To evaluate the feasibility of receiving SC hydration at home **Aim of intervention:** Hydration **Sample size calculation:** No information
Participants	**Recruitment:** from a home palliative care program **Inclusion/exclusion criteria:** Enrolled in the palliative care program **Type of patient:** Advance cancer patients **Age:** No information **Setting:** Home setting **Sex:** No information **Number of participants:** 52
Interventions	**Intervention:** SC hydration, no information on size **Comparator:** None **Fluid type infused:** No information **Duration of intervention:** Median days of infusion was 12 days (range 2-173), until death **Number of infusions:** No information. **Infusion site duration:** No information **Use of hyaluronidase:** No information
Outcomes	**Adverse effects** **Outcome definition:** No information **How was the outcome assessed:** Phone calls at 48h and 7 days to assess adherence and complications. One month after death to explore caregivers' perception of sc hydration. Adverse effects were mild and infrequent.

	All were able to maintain hydration until no longer indication or death. Almost all found it easy to administer the SC hydration (at 48 hours 78% found it easy, at 7 days 96% found it easy)
Notes	

Hussain 1996[26]

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[55]

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.

Lamandé 2004[27]

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, mean volume per day: 1061 +- 292 ml. Infusion site was abdomen 33%, thighs 60%, back 5%, 2% shoulders. **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

Calculations based on numbers from table 1. Table 1 needed to understand, but we cannot bring it here due to copyright.

29/1142= 2,5%	27/1142=2,4%	1,7%
8/184=4,3%	0	0,5%
7,4%	0	1,9%
4%	4%	0
0	0	0

Calculations based on numbers from table 2. Table 2 needed to understand, but we cannot bring it here due to copyright.

3.8%	2.2%	1.8%
3.4%	3.9%	1.1%
75.9%	5.6%	5.6%
0%	0%	0%
1.5%	0.3%	0.6%

Notes Unable to find active email of corresponding author.

Martinez-Riquelme 2005[38]

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, patients were trained to self-administer subcutaneous fluids via a fine 20-G butterfly needle, inserted into the subcutaneous fatty layer of the thigh, upper arm or trunk.

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.

Rodríguez-Campos 2022[36]

Methods	**Publication type:** Journal article **Study design:** Retrospective descriptive study ("reviewed medical records of consecutive patients", n=300) **Country of study:** Colombia **Language of publication:** English **Year of study:** 2017-2018 **Source of funding:** No external funding **Aim of study:** to determine the feasibility of SQ administration of medications and fluids by nonprofessional caregivers to patients at a home-based palliative care program **Aim of intervention:** Hydration and medication **Sample size calculation:** 300 consecutive patients
Participants	**Recruitment:** Consecutive patients **Inclusion/exclusion criteria:** admitted to the palliative home-based program who received treatment using SQ catheters **Type of patient:** Palliative patients, 218 with malignant diseases; 54 non-malignant **Age:** 72 +- 18 years **Setting:** Home setting **Sex:** 60% were women **Number of participants:** 189 who received SC hydration
Interventions	**Intervention:** SC hydration and medication. SC place in right pectoral region in 50.6% of patients, followed by the left pectoral region in 19%, and the right abdominal region in 18.5%. g20-22 for hydration. **Comparator:** None **Fluid type infused:** Normal saline solution was used in 152 (56%), 5% dextrose in 79 (29%), and lactated Ringer's solution in 38 (14%) subjects. In 79 subjects (29%), two or more types of substances were used. **Duration of intervention:** **Number of infusions:** No information. **Infusion site duration:** The median indwelling time of an SQ catheter is 15 days (IQR: 6–40). **Use of hyaluronidase:** No use of hyaluronidase
Outcomes	Infection occurred in 2% of 903 catheter insertions.
Notes	

Schen 1981[56]

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[57]

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[58]

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

Štastná 2009[58]

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, g 22, Placed on the abdomen **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.

Torsheim 1999[34]

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: oedema. **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, g22, on abdomen or thigh, 1 litre was given over 8 hours. **Comparator:** None **Fluid type infused:** NaCl, 5% glucose **Duration of intervention:** 17 infusions 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[35]

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, placed on the abdomen, chest, upper back, thigh, no information on size **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	**<u>Adverse effects</u>** **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[29]

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[40]

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, G23-25, placed on the abdomen, most patients received 1.5 liters per day **Comparator:** None **Fluid type infused:** A combination of NaCl and glucose/dextrose, a few 5% 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

	Duration on the drip 13 patients were on the drip more than 6 days, One patient was on the drip for 22 days.
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.

2.4 Case reports

Kackielo 2000[59]

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.

Lemeray 2012[60]

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.

Mongardon 2008[43]

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[61]

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.

8. Om denne kliniske retningslinje

Denne kliniske retningslinje er udarbejdet på baggrund af en skabelon fra Danske Multidisciplinære Cancer Grupper (DMCG.dk).

Retningslinjen er målrettet klinisk arbejdende sundhedsprofessionelle i det danske sundhedsvæsen og indeholder systematisk udarbejdede udsagn, der kan bruges som beslutningsstøtte til fagpersoner og patienter, når de skal træffe beslutning om passende og korrekt sundhedsfaglig ydelse i specifikke kliniske situationer.

Denne kliniske retningslinje har karakter af faglig rådgivning. Retningslinjerne er ikke juridisk bindende, og det vil altid være det faglige skøn i den konkrete kliniske situation, der er afgørende for beslutningen om passende og korrekt sundhedsfaglig ydelse. Der er ingen garanti for et succesfuldt behandlingsresultat, selvom sundhedspersoner følger anbefalingerne. I visse tilfælde kan en behandlingsmetode med lavere evidensstyrke være at foretrække, fordi den passer bedre til patientens situation.

Man kan ved subkutan væskebehandling bruge enzymet hyaluronidase, der midlertidigt opløser hyaluronan i underhuden. Dette er blevet brugt hyppigt tidligere og bruges stadig regelmæssigt i andre lande. Enzymet øger absorptionen af væske og medicin, som gives subkutant. Hyaluronidase er ikke indregistreret som enkeltstående lægemiddel i Danmark og bruges derfor ikke ved subkutan væskebehandling i Danmark. Ved udarbejdning af disse anbefalinger er der taget højde for, at hyaluronidase ikke bruges i Danmark, og at resultater fra studier om subkutan væskebehandling, hvor der er brugt hyaluronidase, ikke nødvendigvis kan overføres til subkutan væskebehandling, hvor der ikke bruges hyaluronidase.