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A cluster randomised feasibility trial of clinically assisted hydration in cancer patients in the last days of life

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Abstract

Background: The provision of clinically assisted hydration at the end-of-life is one of the most contentious issues in medicine.
Aim: The aim of this feasibility study was to answer the question 'can a definitive (adequately powered) study be done?'
Design: The study was a cluster randomised trial, with sites randomised on a one-to-one basis to intervention 'A' (regular mouth care and usual other care) or intervention 'B' (clinically assisted hydration, mouth care and usual other care). Participants were assessed every 4 h, and data collected on clinical problems, therapeutic interventions and overall survival.
Setting/participants: The study was conducted at 12 sites/'clusters' with specialist palliative care teams (4 cancer centres and 8 hospices), and participants were cancer patients in the last week of life who were unable to maintain sufficient oral fluid intake.
Results: The study achieved its pre-determined criteria for success. Two hundred patients were recruited to the study, and 199 participants completed the study, over a 1-year period. A total of 38.5% participants discontinued clinically assisted hydration due to adverse effects: none of these adverse events were rated as 'severe' or worse in intensity. The primary reasons for discontinuation were site problems ($n = 2$), localised oedema ($n = 13$), generalised oedema ($n = 5$), respiratory secretions ($n = 6$) and nausea and vomiting ($n = 1$).
Conclusion: The results of this feasibility study suggest that a definitive study can be done, but that minor changes are needed to the protocol to standardise the administration of clinically assisted hydration (which may reduce the incidence of certain adverse effects).

Keywords

Fluid therapy, terminal care, neoplasms, cluster analysis

What is already known about the topic?

- The Cochrane systematic review of clinically assisted hydration identified three randomised controlled trials (RCTs) and concluded that 'there are insufficient good-quality studies to inform definitive recommendations'.
- None of the previous RCTs addressed the specific issue of the routine use of clinically assisted hydration at the end-of-life (and until death).
- All of the previous RCTs included patients with dehydration, and the volume of fluid administered was inadequate to maintain hydration (and certainly inadequate to reverse dehydration).

What this paper adds?

- This feasibility study is the first RCT to investigate the routine use of clinically assisted hydration in cancer patients at the end-of-life.

Implications for practice, theory or policy

- The results of this feasibility study suggest that a definitive study can be done.
- The results of the feasibility study should not influence current clinical practice.

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Introduction

The provision of clinically assisted hydration at the end-of-life is one of the most contentious issues in medicine, and indeed within the general population.[1] The reasons for contention include the lack of evidence for or against clinically assisted hydration,[2,3] the disparate opinions of healthcare professionals about clinically assisted hydration and the generally positive opinions of patients and their carers about clinically assisted hydration (and the generally negative opinions about withholding or withdrawing clinically assisted hydration).[4] It is, therefore, unsurprising that the provision of clinically assisted hydration at the end-of-life is extremely variable within clinical practice (i.e. 12%–88% cancer patients in the last week of life).[5] (It should be noted that, in this instance, clinically assisted hydration refers to the medical provision of parenteral fluids (i.e. intravenous and subcutaneous) and not to the medical provision of enteral fluids (e.g. via gastrostomy and via jejunostomy).)

The Cochrane systematic review of medically assisted (also known as clinically assisted) hydration for adult palliative care patients concluded that 'there are insufficient good-quality studies to inform definitive recommendations'.[2] It identified six relevant studies,[6–11] although only three studies were randomised controlled trials (RCTs).[8,9,11] However, none of the RCTs addressed the specific issue of the routine use of clinically assisted hydration at the end-of-life (and until death). Moreover, all of the RCTs included patients with dehydration, and the volume of fluid administered was inadequate to maintain hydration (and certainly inadequate to reverse dehydration).[12]

The purported negative effects of clinically assisted hydration include fluid overload (e.g. peripheral oedema and cardiac failure) and increased fluid-related problems (e.g. nausea and vomiting, and respiratory secretions).[13] In addition, it has been claimed that ketones and other by-products of dehydration could have beneficial effects on the patients' condition (i.e. analgesic effects and sedative effects). The purported positive effects of clinically assisted hydration include patient comfort (e.g. prevention of thirst and prevention of dry mouth) and prevention of dehydration-related problems (e.g. renal failure and hyperactive delirium).[13] However, as intimated above, there is little evidence to support or refute these effects within the medical literature.

Our hypothesis was that adequate (to prevent dehydration) clinically assisted hydration during the last few days of life would maintain renal perfusion, and so prevent accumulation of drugs and toxins, and so prevent the development of hyperactive delirium ('terminal agitation') in individual cancer patients. It should be noted that delirium is one of the most common problems (25%–85% patients),[14] and importantly one of the most distressing problems,[15] encountered during the last few days of life.

Methods

The study was sponsored by the University of Surrey, supported by the Surrey Clinical Research Centre (Clinical Trials Unit) and approved by the London – Bromley Research Ethics Committee (14/LO/1543; 3 October 2014). The study was registered on ClinicalTrials.gov (reference NCT02344927).

Study design

This study was a feasibility study, and so the main objectives were to assess the processes, resources, management and scientific aspects (and also to determine the sample size for a definitive study).[16] The rationale for undertaking a feasibility study was the controversial nature of the research question, the somewhat novel study design (cluster randomised trial) and the somewhat novel consent process (see below).

The rationale for undertaking a cluster RCT was repeated failures in conducting conventional RCTs in cancer patients in the last days of life and previous successes in conducting cluster randomised trials in this specific group of patients.[17,18] For example, Fowell et al.[17] performed a crossover study of the effectiveness of anti-emetics in syringe drivers in dying patients: the focus of this study was on obtaining consent and the influence of individual randomisation versus cluster randomisation. During the individual randomisation phase of the study, 24% patients consented to participate in the study, while during the cluster randomisation phase of the study, 54% patients consented to participate in the study. Another reason for conducting cluster randomised trials is to reduce the risk of 'treatment contamination' within the study sites. It should be noted that cluster randomised trials are well established in other areas of medicine.[19]

Study setting

The study was carried out between February 2015 and February 2016 in four cancer centres and eight hospices in the United Kingdom (see Acknowledgements).[20] Each site constituted a single cluster, and all the participants within a site/cluster received the same intervention (see below). The hospitals had to be cancer centres with a specialist palliative care team with sufficient resources to undertake research, while the hospices had to have a specialist palliative care inpatient unit with again sufficient resources to undertake research.

Participant sampling

All patients within an institution were eligible for inclusion in the study, assuming they met all of the inclusion criteria for the study (and did not meet any of the exclusion criteria for the study). The inclusion criteria were (a) diagnosis of

cancer, (b) age ⩾18 years, (c) estimated prognosis ⩽1 week (clinical assessment by clinical team; specific prognostic tool not utilised) and (d) patient is unable to maintain sufficient oral intake (1 L/day). The exclusion criteria were (a) patient is dehydrated (clinical assessment by clinical team; supporting blood tests not required), (b) patient has hyperactive delirium ('terminal agitation') at present/in last 24 h (clinical diagnosis by clinical team; specific diagnostic tool not utilised), (c) relevant advance directive to refuse treatment, (d) clinical indication for clinically assisted hydration (e.g. hypercalcaemia), (e) clinical contraindication to clinically assisted hydration (e.g. cardiac failure), (f) clinical contraindication to peripheral cannulation, (g) intravenous fluids/subcutaneous fluids/total parenteral nutrition/enteral feeding or fluids already being administered and (h) patient is likely to be transferred to another setting for end-of-life care.

Study interventions

The interventions utilised within this study represent the current standards of care within clinical practice in the United Kingdom. Standard intervention arm 'A' involved continuance of/support with oral intake, regular mouth care and usual management of pain and other symptoms. Standard intervention arm 'B' involved continuance of/support with oral intake, regular mouth care, usual management of pain and other symptoms, and clinically assisted hydration. The parenteral fluids were administered either intravenously or subcutaneously at the discretion of the clinical team (and in accordance with the local policy). The type of fluid administered was dextrose saline (i.e. 4% dextrose and 0.18% sodium chloride), which is recommended in the relevant National Institute for Health and Care Excellence (NICE) guideline.[12] The volume of fluid administered was dependent on the participant's weight, which is again recommended in the relevant NICE guideline.[12] Thus, participants with a weight of <45 kg received 1 L fluid every 24 h, those weighing 45–60 kg were given 1.5 L fluid every 24 h and participants with a weight of >60 kg received 2 L fluid every 24 h. The parenteral fluids were administered either continuously or in boluses at the discretion of the clinical team (and in accordance with the local policy).

Sites were randomised to one or other intervention, and this became the standard of care within the site for the duration of the trial. The randomisation was balanced, and there was separate randomisation for the hospitals and the hospices. The randomisation process was co-ordinated by the clinical trials unit, and the method utilised was computer generation using SAS Proc Plan (SAS Institute Inc., Cary, USA). The study was unblinded due to the nature of the two interventions.

Participant recruitment

During the study, all patients within the sites were preferentially treated with the allocated intervention, irrespective of whether or not they participated in the study (assuming there was no clinical indication for the alternative intervention or contraindication to the allocated intervention). Consent was only sought once the patient was eligible to participate in the study, that is, there was no 'advanced' consent process. Consent was sought from the patient (whenever possible), or advice from a 'personal consultee' when the patient was unable to provide consent, or advice from a 'nominated consultee' when the patient was unable to provide consent and there was no personal consultee (as per the Mental Capacity Act).[21] In this study, the personal consultee was a relation or a friend of the patient, and the nominated consultee was the site Study Guardian (i.e. a senior healthcare professional independent of the research team). Moreover, in patients that were initially able to consent and that were subsequently deemed to have lost capacity, a personal/nominated consultee was required to confirm continued involvement in the study.

Study outcomes

The main objectives were to assess the processes, resources, management and scientific aspects (and also to determine the sample size for a definitive study).[16] The predetermined criteria for success were (a) recruitment – 200 patients in 1 year, (b) retention – ⩾67% participants complete the study, (c) adherence to study procedures – ⩾67% nursing observations are completed and (d) safety of study interventions – ⩽50% participants have discontinued clinically assisted hydration due to treatment-related adverse events.

The choice of 'cut-offs' was somewhat pragmatic, but guided by a pre-study service evaluation undertaken at the main site.

The primary clinical outcome of the feasibility study was the development of hyperactive delirium ('terminal agitation'), which was deemed to occur if the patient developed a score of ⩾2 on the modified Richmond Agitation and Sedation Scale (m-RASS),[22,23] and the clinical team contemporaneously administered appropriate medication for hyperactive delirium (i.e. antipsychotic drug and sedative drug). Other clinical outcomes included the development of other end-of-life care problems (audible respiratory secretions, shortness of breath, nausea and vomiting, and pain), utilisation of medication to treat end-of-life care problems (regular medication and as-required medication), adverse events and date/time of death.

Data collection

Patients were routinely assessed every 4 h for common end-of-life problems (i.e. hyperactive delirium/'terminal agitation', audible respiratory secretions/'death rattle', nausea and vomiting, pain and shortness of breath), which were recorded as either present or absent, with the exception of agitation which was scored using the m-RASS.

Patients were also assessed for adverse effects (especially relating to the clinically assisted hydration). All assessments were undertaken by the clinical team (nursing team), as were decisions to utilise medications to treat such end-of-life care problems (nursing and medical teams). End-of-life care problems were managed according to local protocols, and the indications for/scheduling of all medication were recorded. Patients were followed up until death or for a maximum of 14 days (end of study).

Sample size

The sample size of 200 was based on a recommendation for sample sizes for feasibility studies involving a cluster randomised methodology:[24] the number of clusters was based on the required sample size and the fixed study duration (1 year). Each site was encouraged to recruit as many participants as possible (to ensure that the study was completed within 1 year).

Data analysis

Descriptive statistics were used to report the criteria for success of the study: the relevant figures were calculated and presented as absolute numbers and percentages. Standard statistical analyses were performed on the clinical outcomes, and the intracluster correlation coefficient (ICC) was calculated for the main clinical outcomes in order to help to determine the sample size for the definitive study.

Due to the cluster randomisation design of the trial, experimental units within each cluster were correlated, and this correlation was properly accounted for in the analysis to avoid bias in statistical inferences. All analyses were conducted on the Intention-To-Treat (ITT) population, and analyses were not required on a Per Protocol (PP) population as there were no protocol violations.

The primary clinical outcome, the dichotomy of occurrence or not of hyperactive delirium, was analysed as the response variable with intervention as a fixed effect predictor and cluster as a random effect predictor in a generalised linear mixed model with logit link and Kenward–Roger degrees of freedom adjustments using PROC GLIMMIX in SAS version 9.4. Other dichotomous secondary clinical outcomes, such as occurrence of audible respiratory secretions at least once daily or not, occurrence of shortness of breath at least once daily or not, occurrence of nausea and vomiting at least once daily or not, occurrence of pain at least once daily or not, having received regular medication at least once daily or not and having received as-required medication once daily or not, were analysed using analogous methods.

The survival time of each participant from randomisation was statistically contrasted between the two intervention groups using an approach that accounted for the within-cluster correlation using a shared frailty model, where cluster effects were incorporated into the model as independent and identically distributed random variables. In this model, the survival time was analysed in a COX regression model with intervention and intervention by survival time interaction as fixed effects predictors and cluster as random effects predictor using SAS PROC PHREG. Participants who survived until the end of day 14 were right censored. The time from randomisation to starting pro re nata (prn) medication for hyperactive delirium and audible respiratory secretions were analysed using analogous methods.

Results

Recruitment and retention

A total of 200 patients were recruited to the study within 1 year (see Table 1), and 199 (99.5%) participants completed the study (see Figure 1). One patient was withdrawn due to an improvement in their condition, while 13 (6.5%) patients were still alive at the end of the study (i.e. 14 days after entry into the study). Informed consent was received from 16 (8%) patients, 'advice' obtained from 161 (80.5%) personal consultees and advice obtained from 23 (11.5%) nominated consultees.

Adherence to study procedures

In total, 93.6% nursing observations were completed in the clinical observation document and there was no discernible pattern to the 'missing' observations. Feedback from focus groups confirmed that nursing staff felt that the document was easy to complete, and that completion of the document (and related assessments) did not have a negative impact on the care of the patient. Indeed, nurses noted that carers were often reassured by the regular completion of the document.

Only 36.5% participants received clinically assisted hydration, and this reflects the fact that a large (multi-site) hospice was randomised to intervention arm 'A' (non-clinically assisted hydration group) and no similar-sized hospice was randomised to intervention arm 'B' (clinically assisted hydration group). Indeed, 27% of total participants were recruited from the relevant hospice. All participants received the correct intervention and all participants in the clinically assisted hydration group received the correct type/volume of fluid (as per protocol).

Safety of study interventions

In total, 28 (38.5%) participants discontinued clinically assisted hydration due to adverse effects. The primary reasons for discontinuation were site problems ($n = 2$), localised oedema ($n = 13$), generalised oedema ($n = 5$), respiratory secretions ($n = 6$), nausea and vomiting

Table 1. Demographic data.

	All subjects ($n = 200$)	CAH group ($n = 73$)	Non-CAH group ($n = 127$)	p-value
Age				
Median (range)	74 years (28–98)	72 years (28–96)	75 years (39–98)	0.4916
Gender				
Female	116 (58%)	43 (59%)	73 (57%)	0.8443
Male	84 (42%)	30 (41%)	54 (43%)	
Ethnicity				
Asian/Asian British	1 (0.5%)	0 (0.0%)	1 (0.8%)	0.7918
Black/Black British	1 (0.5%)	0 (0.0%)	1 (0.8%)	
White	185 (92.5%)	67 (91.8%)	118 (92.9%)	
Mixed	2 (1.0%)	1 (1.4%)	1 (0.8%)	
Not stated	11 (5.5%)	5 (6.8%)	6 (4.7%)	
Significant comorbidities				
Yes	151 (75.5%)	58 (79.5%)	93 (73.2%)	0.3245
No	49 (24.5%)	15 (20.5%)	34 (26.8%)	
Cancer diagnosis				
Breast	15 (7.5%)	6 (8.2%)	9 (7.1%)	0.2949
Endocrine	5 (2.5%)	0 (0.0%)	5 (3.9%)	
Gastrointestinal	67 (33.5%)	31 (42.4%)	36 (28.3%)	
Gynaecology	17 (8.5%)	4 (5.5%)	13 (10.2%)	
Haematology	11 (5.5%)	3 (4.1%)	8 (6.3%)	
Head and neck	4 (2.0%)	1 (1.4%)	3 (2.4%)	
Lung	30 (15.0%)	8 (11.0%)	22 (17.3%)	
Neurology	10 (5.0%)	6 (8.2%)	4 (3.2%)	
Skin	8 (4.0%)	4 (5.5%)	4 (3.2%)	
Unknown	12 (6.0%)	6 (8.2%)	6 (4.7%)	
Urology	15 (7.5%)	3 (4.1%)	12 (9.5%)	
Other	6 (3.0%)	1 (1.4%)	5 (3.9%)	

CAH: clinically assisted hydration.

($n = 1$) and not recorded ($n = 1$). Additional adverse events were reported in 11 participants from the clinically assisted hydration group (including 2 of the withdrawn participants) and in 2 participants from the non-clinically assisted hydration group (see Table 2). None of the adverse events in the clinically assisted hydration group were assessed as being severe, but the seizure that occurred in one participant from the non-clinically assisted hydration group was assessed as being life-threatening.

Clinical outcomes

Data on hyperactive delirium ('terminal agitation') are shown in Table 3, while data on other end-of-life care problems are shown in Table 4. The frequency of primary clinical outcome was similar in the two groups, but there was a non-significant delay in the need to dispense relevant as-required medication in the clinically assisted hydration group (65.06 vs 48.49 h, $p = 0.0989$). It should be noted that the primary clinical outcome underestimated the incidence of hyperactive delirium based on the frequency of usage of regular and as-required medication to treat hyperactive delirium (see Table 3). The incidence of audible upper airway secretions ('death rattle') was also similar in the two groups, but in this case there was a significant delay in the need to dispense relevant as-required medication in the clinically assisted hydration group (116.00 vs 57.82 h, $p < 0.001$).

Figure 2 shows the Kaplan–Meier survival curves for the two groups. The unadjusted (for clustering) median survival in the non-clinically assisted hydration group was 2.8958 days (95% confidence interval: 2.4306–4.0417 days), while the unadjusted median survival in the clinically assisted hydration group was 4.2639 days (95% confidence interval: 3.3472–6.1583 days): the difference in median survival was statistically significant ($p = 0.0387$). The hazard ratio for survival at 3 days in the clinically assisted hydration group was 0.358 (95% confidence interval: 0.219–0.585). It should be noted that the latter statistic accounts for clustering.

Discussion

Main findings of the study

The study achieved all of its pre-determined criteria for success, and so a definitive study is being planned in order to further evaluate the role of clinically assisted hydration in cancer patients in the last days of life.

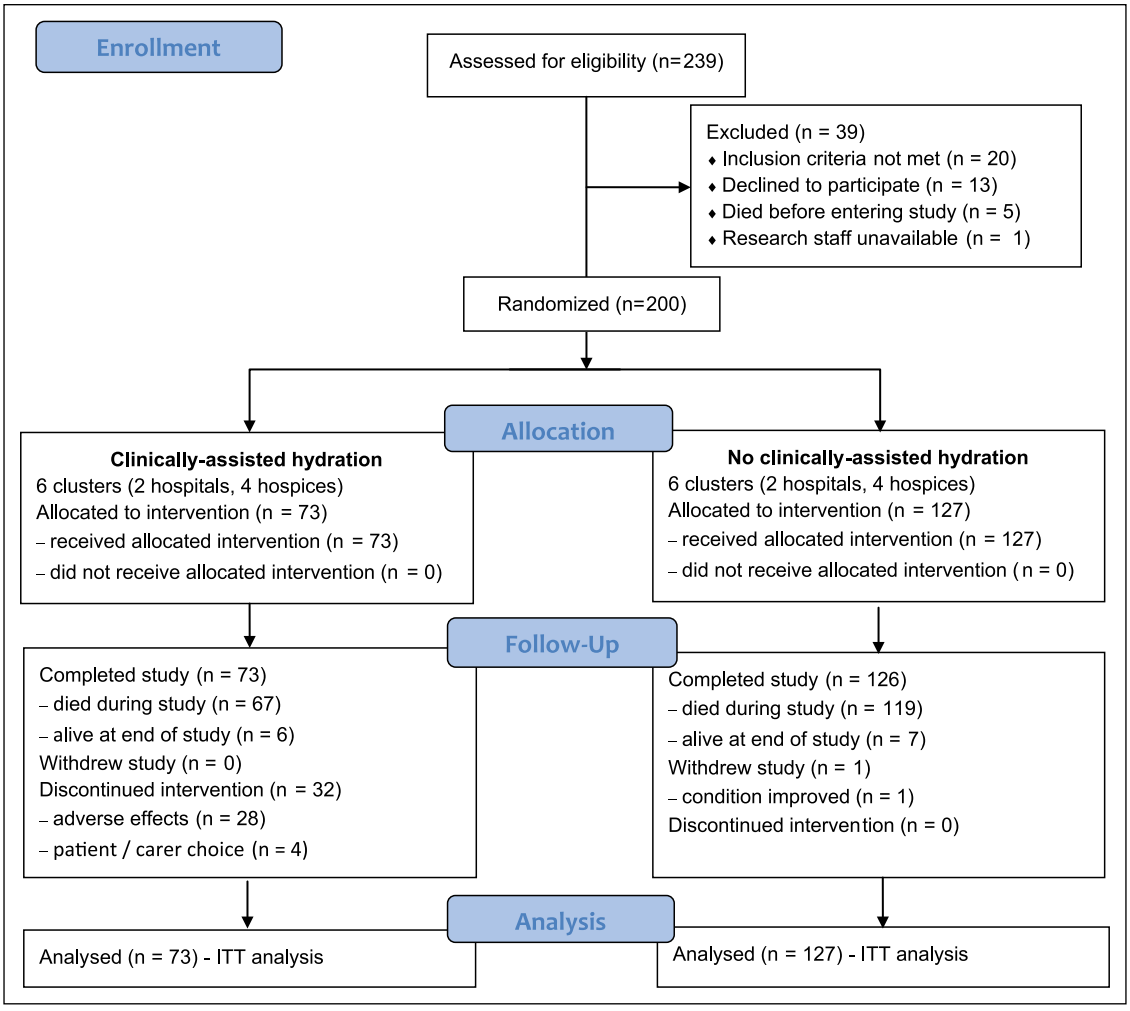

Figure 1. Consort diagram.

The protocol for the definitive study will be similar to that for the feasibility study (study design and consent process), although there will be greater standardisation of the method of administering the clinically assisted hydration and of the criteria for discontinuing the clinically assisted hydration (see below). The primary clinical outcome of the feasibility study significantly underestimated the incidence of hyperactive delirium (based on the use of as-required medication for hyperactive delirium). Thus, we will use a different primary endpoint for the definitive study, that is, time to first dose of as-required medication for hyperactive delirium (which is a surrogate for the time to development of hyperactive delirium). The new primary endpoint was chosen as it is clinically relevant, and the observed difference between interventions is potentially clinically important.

The sample size for the definitive study has been calculated using the ICC for the new primary endpoint; the definitive study will involve 12 study sites (clusters) and a total of 600 patients (i.e. 50 patients per study site). Furthermore, recruitment will be 'balanced' in the definitive study (as opposed to 'competitive' in the feasibility study).

Patients and their carers were invariably positive about the study,[25] irrespective of the allocated intervention at the study site. Thus, only 13 eligible patients/carers in total declined to take part in the study. Furthermore, no patients withdrew consent during the study and no carers withdrew support for patients that had lost capacity during the study (in their role as personal consultee).

Twenty-eight (38.5%) participants discontinued clinically assisted hydration due to adverse effects, which may have well influenced the primary and secondary clinical outcomes. The most common problem ($n = 13$) was localised oedema: the clinical teams were allowed to administer the fluids as per local policy, but a standardised protocol will be used in the definitive study to ensure that the cannulas are sited in optimal positions (i.e. lower abdomen or upper chest rather than arm or leg),[26] and that the fluids are administered at optimal rates (i.e. continuous infusions

Table 2. Adverse events (excluding primary reason for withdrawal).

Non-CAH group		
Adverse event	Number participants ($n = 127$)	Severity
Seizure	1	Life threatening
Fall	1	Mild
CAH group		
Adverse event	Number participants ($n = 73$)	Severity
Localised oedema	4	Mild – all
Headache	1	Moderate
Seizure	1	Moderate
Skin rash	1	Moderate
Vaginal bleeding	1	Moderate
Jaw swelling	1	Mild
Nausea	1	Mild
Respiratory secretions	1	Mild
Shortness of breath	1	Mild
Site reaction	1	Mild
Urinary tract infection	1	Mild

CAH: clinically assisted hydration.

rather than bolus infusions). The second most common problem ($n = 6$) was upper respiratory secretions: in view of the data from this study and analogous date from other studies,[27,28] clinicians will be encouraged not to discontinue clinically assisted hydration for this reason in the definitive study (see below).

Clinical outcomes

The study was not powered to compare clinical outcomes between the two intervention arms, and so the results relating to these clinical outcomes need to be interpreted with extreme caution.

The data suggest that clinically assisted hydration may not reduce the frequency of hyperactive delirium, but that it does at least appear to delay the onset of this very distressing clinical problem.[15] The latter is important in terms of the patient's quality of life, the carer's experience and the need to use potentially sedative drugs, which constrain communication between the patient and their carers.[1] However, the exact effect of clinically assisted hydration on hyperactive delirium needs to be determined in a larger (definitive) study, where more participants receive the intervention during the study and more participants continue with the intervention until death. It should be noted that the primary endpoint underestimated the incidence of hyperactive delirium, since many patients developed agitation outside of the formal assessment times (and the agitation responded to treatment by the next formal assessment time).

Equally, the data suggest that clinically assisted hydration may not affect the frequency of upper airway secretions ('death rattle'), but that it does at least delay the onset of this again very distressing clinical problem. Interestingly, other researchers have reported no association between hydration/dehydration and the frequency of upper airway secretions.[27,28] Nevertheless, many clinicians believe that clinically assisted hydration can cause/aggravate this problem,[13] and 21% withdrawals from the study were primarily due to the development of this problem.

The data suggest that clinically assisted hydration may prolong the median survival of cancer patients in the last days of life. For some patients (and families), living an extra day or so may be extremely important, especially if that period is not associated with troublesome end-of-life care problems. Reassuringly, our data suggest that most patients were generally asymptomatic/well symptom controlled in the last days of life (not all data shown). Nevertheless, for other patients, living an extra day or so may be an undesirable consequence. Again, the exact effect of clinically assisted hydration on survival needs to be determined in a larger (definitive) study. Of note, a recent observational study reported decreased survival in 'less hydrated' cancer patients.[29]

Weaknesses of the study

A weakness of the study was the reliance on the clinical assessments rather than the use of validated assessment instruments (or diagnostic investigations). For example, one of the inclusion criterion was 'prognosis of <1 week', and this was assessed clinically. A number of patients exceeded their predicted prognosis (i.e. $\leqslant 1$ week), and the accuracy of prognostication may have been improved with the use of a validated assessment tool. (In the definitive study, we intend to utilise a validated assessment tool.)

Similarly, one of the exclusion criterion was 'patient is dehydrated', and this was again assessed clinically (i.e. history and examination). However, the clinical features of dehydration are somewhat unreliable, although it should be noted that standard laboratory investigations can also be unreliable.[30] (In the definitive study, we intend to utilise duplicate (independent) clinical assessments of hydration.)

The same criticism can be levelled at the use of clinical assessments to determine the presence of relevant clinical problems (e.g. hyperactive delirium and upper airway secretions). The rationale for the reliance on clinical assessments was to limit any disruption to end-of-life care and to minimise the burden on patients, carers and the healthcare professionals. Indeed, the study aimed to replicate as much as possible 'usual' end-of-life care in the United Kingdom.

Table 3. Data on hyperactive delirium.

Endpoint	CAH group ($n = 73$)	Non-CAH group ($n = 127$)	Comments
Patients with m-RASS score ⩾2 and receiving prn medication for agitation within 1 h	13 (17.8%)	21 (16.5%)	Primary endpoint Absolute numbers
Probability[a] (SE) of m-RASS score ⩾2 and receiving prn medication for agitation within 1 h	0.158 (0.043)	0.128 (0.030)	Primary endpoint Odds ratio[b] 1.273 (95% CI: 0.136–11.870, $p = 0.805$) Intra-cluster correlation coefficient (ICC) = 0.3228
Mean (SE) m-RASS score[c]	0.154 (0.042)	0.138 (0.038)	Mean difference −0.017 (95% CI: −0.156 to 1.22, $p = 0.776$)
Maximum m-RASS score[c]			Absolute numbers
0	30 (41.1%)	49 (38.6%)	
1	25 (34.2%)	53 (41.7%)	
2	13 (17.8%)	21 (16.5%)	
3	4 (5.5%)	4 (3.1%)	
4	1 (1.4%)	0 (0%)	
Patients given prn medication for agitation	48 (65.7%)	82 (64.5%)	Absolute numbers
Probability[a] (SE) of receiving prn medication for agitation	0.699 (0.053)	0.592 (0.043)	Odds ratio[b] 1.600 (95% CI: 0.357–7.173, $p = 0.4895$)
Patients dispensed regular medication for agitation	34 (46.5%)	75 (59.1%)	Absolute numbers
Probability[a] (SE) of receiving regular medication for agitation	0.545 (0.058)	0.425 (0.044)	Odds ratio[b] 1.619 (95% CI: 0.219–11.940, $p = 0.596$)
Mean (SE) time to first dose of prn medication for agitation	65.06 (7.92) h	48.49 (6.05) h	Mean difference −16.57 (95% CI: −36.308 to 3.157, $p = 0.0989$) ICC = 0.005

CAH: clinically assisted hydration, m-RASS: modified Richmond Agitation Sedation Scale, SE: standard error, CI: confidence interval, prn: pro re nata.
[a]Probability values range from 0 (0%) to 1 (100%).
[b]Odds ratios adjusted for clustering.
[c]m-RASS scores range from 0 ('alert or calm') to 4 ('combative').

Table 4. Data on other end-of-life problems.

Endpoint	CAH group ($n = 73$)	Non-CAH group ($n = 127$)	Comments
Patients with audible respiratory secretions ('death rattle') during study	39 (53.4%)	66 (52.0%)	Absolute numbers
Number of days with audible respiratory secretions			Absolute numbers
0	34 (46.6%)	61 (48.0%)	
1	20 (27.4%)	36 (28.3%)	
2	12 (16.4%)	11 (8.7%)	
⩾3	7 (9.6%)	19 (15.0%)	
Mean (SE) time to experiencing audible respiratory secretions	116.000 (11.114) h	57.818 (8.543) h	Mean difference 58.182 (95% CI: 30.380–85.983, $p < 0.001$)
Patients prescribed prn medication for audible respiratory secretions during study	37 (50.7%)	56 (44.1%)	Absolute numbers
Patients prescribed regular medication for audible respiratory secretions during study	16 (21.9%)	31 (24.4%)	Absolute numbers
Probability[a] (SE) of experiencing audible respiratory secretions at least once daily	0.167 (0.044)	0.201 (0.036)	Odds ratio[b] 0.796 (95% CI: 0.420–1.510, $p = 0.425$)
Probability[a] (SE) of experiencing shortness of breath at least once daily	0.084 (0.032)	0.111 (0.028)	Odds ratio[b] 0.732 (95% CI: 0.356–1.504, $p = 0.309$)
Probability[a] (SE) of experiencing nausea and vomiting at least once daily	0.030 (0.020)	0.045 (0.018)	Odds ratio[b] 0.665 (95% CI: 0.186–2.378, $p = 0.483$)
Probability[a] (SE) of experiencing pain at least once daily	0.285 (0.053)	0.236 (0.038)	Odds ratio[b] 1.292 (95% CI: 0.619–2.695, $p = 0.443$)

CAH: clinically assisted hydration, SE: standard error, CI: confidence interval, prn: pro re nata.
[a]Probability values range from 0 (0%) to 1 (100%).
[b]Odds ratios adjusted for clustering.

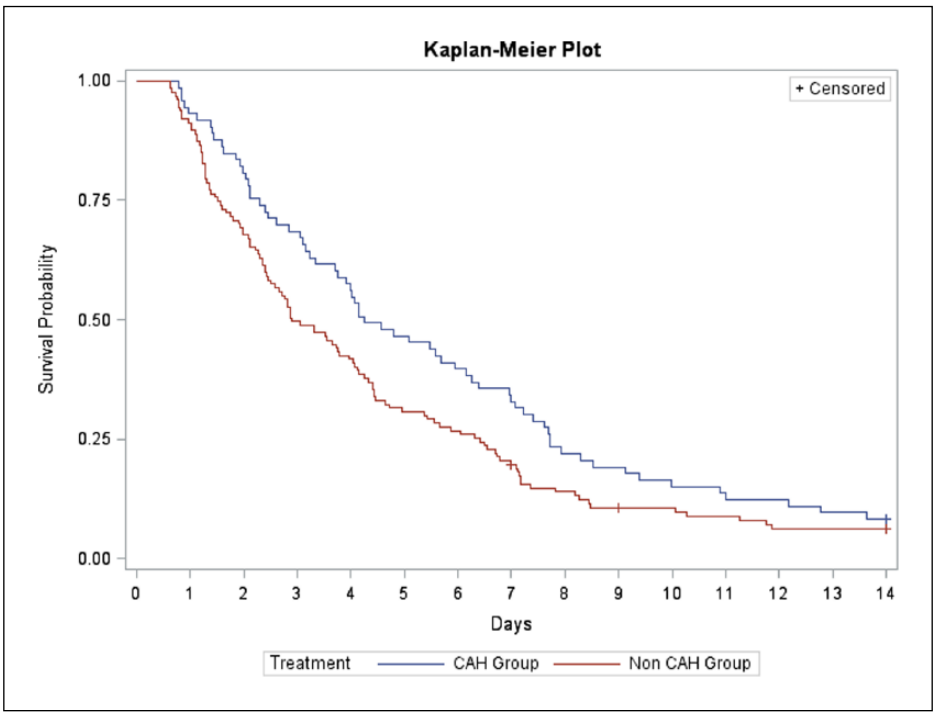

Figure 2. Kaplan–Meier survival curves.

One of the main weaknesses of the study is the unequal distribution of patients between the intervention arms (i.e. 36.5% patients in clinically assisted hydration group and 63.5% patients in the non-clinically assisted hydration group). The main reason for the disparity was the size of the units, and so the ability to recruit participants. In the definitive study, there will be a limit on the number of participants recruited from each site in order to ensure a more even distribution of patients in the intervention arms.

In terms of generalisability and allowing for the aforementioned limitations, the study population appeared to be representative of the cancer patients receiving end-of-life care at the study sites (and of general population of cancer patients at the end-of-life in the United Kingdom). However, there were relatively few non-white participants, although we are not aware of any reason why non-white persons should respond differently to clinically assisted hydration.

What the study adds

This study confirms that appropriately designed RCTs can be conducted in patients in the last days of life. Such studies need to be undertaken, so that we ensure that our practice is evidence-based, and that we provide the best possible end-of-life care to our patients and their carers. Moreover, this study supports the use of cluster randomised trials in the palliative care/end-of-life care setting.

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Data sharing

The data are stored at the Surrey Clinical Research Centre (University of Surrey): the data can be accessed via the Chief Investigator/corresponding author. The study protocol can be accessed from the Surrey Clinical Trials Unit website (http://ctu.surrey.ac.uk/).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

The study was conducted according to the World Medical Association Declaration of Helsinki.

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