Hydration and symptoms in the last days of life

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Submitted

ABSTRACT

Background. At the end of life oral fluid intake is often reduced. Consensus about the most appropriate management for terminally ill patients with limited oral fluid intake is lacking. The debate about (artificial) hydration has mostly focused on two distinct symptoms in particular; death rattle, which has been linked to over-hydration at the end of life, and terminal restlessness, which has been linked to under-hydration at the end of life. The aim of this study is to investigate to what extent the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness.

Methods. We performed a multicentre prospective observational study in eight hospitals and five hospices/palliative care units (PCU's). We collected data on the occurrence of death rattle and terminal restlessness, fluid intake and opioid use of patients who were expected to die within a few days or hours.

Results In total, 371 patients were included (59% of all deaths during the study period). Death rattle was reported at least once in 40% (n=149) of patients during the dying phase, and in 35% (n=130) of patients during the last 24 hours of life. The prevalence of death rattle increased with death coming nearer and was not associated with the amount of fluid intake during the days before dying. Terminal restlessness was reported in 26% of patients (n=96) during the dying phase and in 13% (n=49) of patients during the last 24 hours of life. Terminal restlessness occurred almost evenly throughout the dying phase and was not associated with a lower amount of fluid intake during the days before dying. Terminal restlessness during the last 24 hours of life was associated with a higher amount of fluid (i.e. > 250ml/day) during 48-25 hours before death.

Conclusions. Caution with fluid intake to prevent development of death rattle does not seem to be necessary. Our study suggests that a higher amount of fluid intake during 48-25 hours before death may be associated with the occurrence of terminal restlessness during the last 24 hours of life. Actively providing dying patients with artificial fluid therefore does not seem to be beneficial.

INTRODUCTION

Most patients with a deteriorating chronic illness have a reduced oral intake at the end of life. This may be due to illness- or treatment-related symptoms or complications, such as dysphagia, nausea or vomiting, generalized weakness, and, in the last days of life, to a decreased level of consciousness or a loss of desire to drink[1 2]. The evidence that artificial hydration (AH) may be beneficial when patients have a reduced oral intake in the last days of life is limited and inconclusive[3-5]. Common arguments against AH are that it may increase the risk of complications such as oedema, ascites, and death rattle[1 6 7]. On the other side, the most commonly mentioned benefits of AH are that hydration may alleviate patients' feelings of thirst and reduce the risk of delirium or terminal restlessness[1 5 6 8-10]. Opinions vary on whether or not AH prolongs the dying process[1 5 11 12]. As a result of these opposing arguments, attitudes whether or not AH should be used at the end of life vary among professional caregivers[5-7 13]. Professional caregivers working in palliative care tend to be more reserved about the benefits of AH than other professionals: most of them do not believe that hydration contributes to the alleviation of symptoms or prolongs survival[10 13]. Moreover, many of them are concerned about the additional burden of AH in the last week of life[10 13].

The debate about possible benefits of AH has focused especially on two distinct symptoms in particular; death rattle and terminal restlessness. Death rattle due to respiratory tract secretion is a common symptom with a prevalence of 35% among dying patients and has been linked to over-hydration at the end of life[5 14 15]. Terminal restlessness, an agitated delirium at the end of life, is a common indication for palliative sedation and has been linked to under-hydration at the end of life[5 7 8 16-18]. The aim of this study is to investigate to what extent the amount of fluid intake, preceding and during the dying phase, is related to the occurrence of death rattle and terminal restlessness. The dying phase is defined as the phase when death is expected to occur within hours or days[19 20].

METHOD

Study design and population

We performed a multicentre prospective observational study in patients, 18 years or older, who were, according to the multidisciplinary care team, likely to die within a few days. Data were collected in 8 hospitals (one to three wards per hospital) and five hospices, including three palliative care units in nursing homes (PCUs), in the Netherlands. Data collection took place between November 2012 and November 2013. The study was approved by the Medical Ethics Research Committee of the Erasmus MC, University Medical Centre Rotterdam.

Data collection

Anonymous data were collected using a digital version of the Care Program for the Dying (CPD), a Dutch instrument for multidisciplinary care for patients in the dying phase that was originally based on the Liverpool Care Pathway for the dying patient[21]. It was adapted to the Dutch language and healthcare system. The CPD is started when the multidisciplinary team agrees that the patient is likely to die within a few days and consists of three parts in which different data are recorded by nurses and physicians. For this study, the CPD was supplemented with questions about death rattle, terminal restlessness, patients' fluid intake and use of opioids. We used the following data from the first part of the CPD, reflecting patient characteristics and the patient's situation at the start of the CPD: diagnosis (cancer, non-cancer), gender, date of birth, date and time of the start of the CPD, level of consciousness (conscious, semi-conscious, unconscious) and prevalence of restlessness, confusion and respiratory tract secretions. Further, we used data from questions that were added to part 1, about patients' opioid use during the last day before the start of the CPD, and their total fluid intake (oral, intravenous (IV) and via feeding tube) during the last week and during the last day before the start of the CPD. Questions that were added to the second part of the CPD, reflecting the patient's situation from the start of the CPD until death, concerned total fluid intake, opioid use, occurrence of death rattle and terminal restlessness, all per 4 hourly intervals. From the third part of the CPD, reflecting the situation after the patient's death, we used data about the date and time of the patient's death and the provision of sedation during the dying phase. See the appendix for a detailed description of the variables that were used for this study.

Analysis and statistics

Patients were excluded from the study if data were missing on the date and time of the start of the CPD, the date and time of death or for more than 6 consecutive measurements (CPD, part 2).

Duration of the dying phase was calculated using the start date and time of the CPD and the date and time of the patient's death. *Total fluid intake* was based on the intake of oral fluid, IV fluid as well as fluid intake via a feeding tube. Nurses estimated patient's oral intake during the week before the start of the CPD; during the last day before the start of the CPD, and during the dying phase. The fluid intake by different routes was added per period of time and scored into 3 categories: 0-499 millilitres (ml) per day, 500-999ml per day, ≥1000ml per day for the periods preceding the start of the CPD; and 0-249ml per day, 250-499ml per day, ≥500ml per day during the dying phase. *Opioid doses* were recalculated to the morphine equivalent daily dose (MEDD) (mg/d) according to published equianalgesic dose tables[22 23]: oral morphine 60 mg/day = parental morphine 20 mg/day = transdermal/parenteral fentanyl 25 µg/hour = oral oxycodone 40 mg/day = parental hydromorphone 4 mg/day = transdermal buprenorphine 26 µg/ hour.

In case the dying phase had a duration longer than 48 hours, *fluid intake and opioid dose during 48-25 hours before death* (i.e. the last day preceding the last 24 hours of life) were calculated using the 4 hourly consecutive measurements from part 2 of the CPD. In case the dying phase had a duration between 24 and 48 hours, fluid intake and opioid dose were calculated using data concerning the intake/dose during the last day before the start of the CPD and the 4 hourly information from the consecutive measurements from part 2 of the CPD. In case the dying phase had a duration shorter than 24 hours, fluid intake and opioid dose were based on the data concerning the intake/dose during the last day before the start of the CPD (figure 1). *Death rattle* occurrence was assessed by the attending nurse using the scoring scale as proposed by Back et al.[24]. This scoring scale records the experienced volume of death rattle: 0. inaudible; 1. audible only very close to the patient; 2. clearly audible at the end of the bed, in a quiet room; 3. clearly audible at the door of the room (about 20

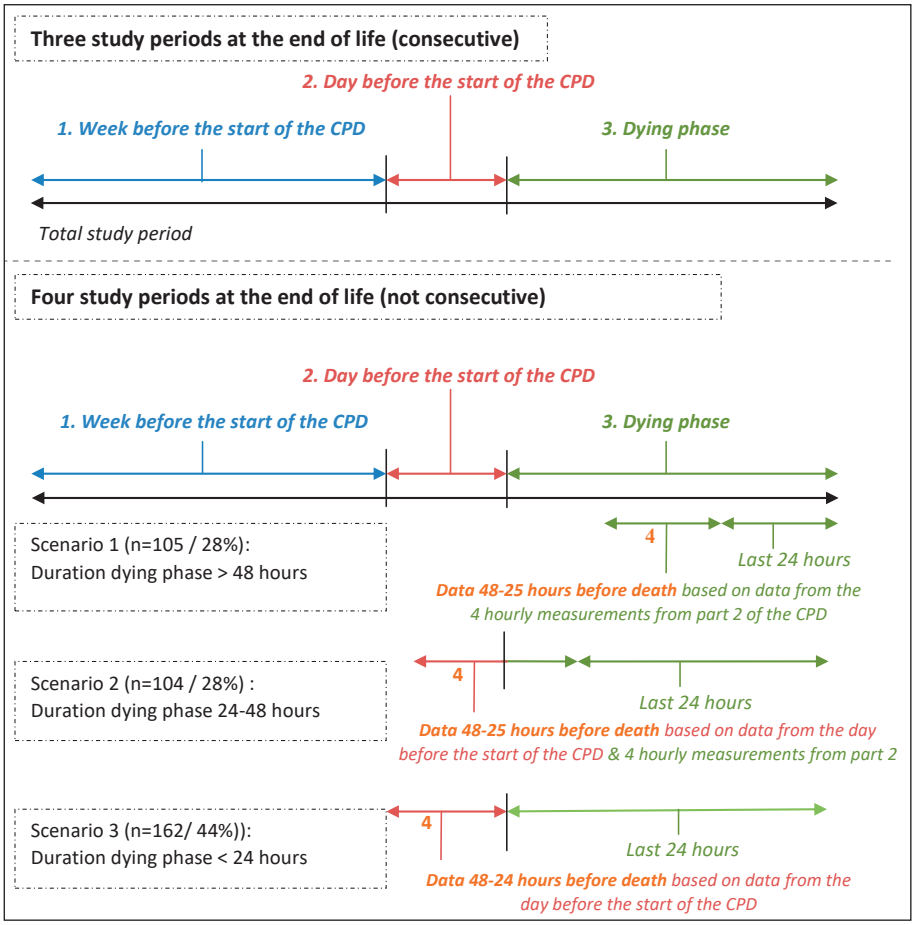

Figure 1. Data collection in relation to the moment of dying

feet/ 10 meter), in a quiet room. In this study a patient was considered to have death rattle when there was a score of ≥2 on at least one 4 hourly measurement during the dying phase. *Terminal restlessness* occurrence was assessed by the attending nurse using the calmness scale of the Vancouver Interaction and Calmness Scale (VICS)[25]. The calmness scale consists of five items: 1. patient appears calm; 2. patient appears restless; 3. patient appears distressed; 4. patient is moving around uneasily in bed; 5. patient is pulling at lines/tubes. Each item is scored on a 6-point Likert-scale (strongly agree, agree, mildly agree, mildly disagree, disagree, strongly disagree). In this study, a patient was considered to experience terminal restless when, focusing on statements 2-5, two statements were scored with 'strongly agree' or 'agree' on at least one 4 hourly measurement, or when at least one statement was scored with 'strongly agree' or 'agree' on at least two consecutive measurements.

Associations between the occurrence of symptoms and patients' fluid intake (i.e. during the week and day before the start of the CPD and during 48-25 hours before death) and other characteristics, including patients' gender, age at death, diagnosis, place of death, duration of the dying phase, level of consciousness at the recognition of the dying phase and opioid use (i.e. during the day before the start of the CPD and during 48-25 hours before death) were analysed using Chi-Square or Mann-Whitney tests, where appropriate. All analyses were performed using SPSS for Windows version 22.0 (SPSS, Inc. Chicago, IL).

RESULTS

Patient characteristics

During the study period 631 patients died in the participating care settings. The CPD was initiated for 476 patients (75% of all deaths), 371 of whom were included in this study (59% of all deaths). One hundred and five patients could not be included; 49 due to missing data about the date and time of the start of the CPD and/or death and 56 due to missing data for more than 6 consecutive 4 hourly measurements (part 2 of the CPD).

The included patients had a mean age of 72 years, almost half of them were male and 79% had been diagnosed with cancer (table 1). Forty-four percent of patients died in the hospital, 56% in the hospice. The median duration of the dying phase was 25 hours for all patients, 23 hours for patients dying in a hospital and 29 hours for patients dying in a hospice. Twenty-eight percent of patients had a duration of the dying phase longer than 48 hours, 28% had a duration between 24-48 hours and 44% had a duration shorter than 24 hours. At the start of the CPD, 22% of the patients were unconscious, 36% were restless, 24% were confused and 19% presented with respiratory tract secretions. Seventy-six percent of the patients used opioids during the last day before the start of the CDP and 93% during the dying phase.

Table 1. Patient characteristics (n=371)

	N (%)	
Gender		
Male	181 (49%)	
Female	190 (51%)	
Age at death (years: mean, SD)		72 (14)
Diagnosis		
Cancer	289 (79%)	
Non-cancer	76 (21%)	
Place of death		
Hospital	164 (44%)	
Hospice	207 (56%)	
Duration of the dying phase (hours: median, range)		25, 0-279
Symptoms at the start of the CPD		
Level of consciousness		
Conscious	112 (30%)	
Semi- conscious	175 (47%)	
Unconscious	80 (22%)	
Restlessness	132 (36%)	
Confusion	86 (24%)	
Respiratory tract secretions	68 (19%)	
Treatment		
Opioid use during the last day before the start of the CPD	282 (76%)	
Morphine equivalent daily dose (mg/24h) (median, range)		75 (2-4200)
Opioid use during the dying phase	345 (93%)	
Morphine equivalent daily dose (mg/24h) (median, range)		108 (0-10790)
Use of palliative sedation during the dying phase	162 (44%)	
Fluid intake		
Total daily fluid intake last week before start of the CPD (ml) (median, range)		625 (125-3375)
0-499ml per day	74 (22%)	
500-999ml per day	117 (35%)	
≥1000ml per day	144 (43%)	
Total daily fluid intake last day before start of the CPD (ml) (median, range)		625 (125-2875)
0-499ml per day	187 (55%)	
500-999ml per day	70 (21%)	
≥1000ml per day	81 (24%)	
Total daily fluid intake during the dying phase (ml) (median, range)		250 (6-2250)
0-249ml per day	257 (69%)	
250-499ml per day	61 (16%)	
≥500ml per day	53 (15%)	
Total daily fluid intake 48-25 hours before death (ml) (median, range)		334 (42-2500)
0-249ml per day	190 (51%)	
250-499ml per day	44 (12%)	
≥500ml per day	121 (33%)	

Table 2. Detailed information concerning fluid intake during the last period of life

	Total (n=371)	Hospital (n=164)	Hospice (n=207)
Week before the start of the CPD			
Orally			
N (%) Yes	302 (81%)	121 (74%)	181 (87%)
median-range	625ml (125-1000ml)	625ml (125-1000ml)	625ml (125-1000ml)
IV			
N (%) Yes	90 (24%)	85 (52%)	5 (2%)
median-range	1250ml (250-1500mlL)	1250ml (250-1500mlL)	750ml (750-750ml)
Tube			
N (%) Yes	23 (6%)	18 (11%)	5 (2%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	750ml (250-1500ml)
Day before the start of the CPD			
Orally			
N (%) Yes	255 (69%)	106 (65%)	149 (72%)
median-range	125ml (125-1000ml)	625ml (125-1000ml)	125ml (125-1000ml)
IV			
N (%) Yes	94 (25%)	90 (55%)	4 (2%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	750ml (250-750ml)
Tube			
N (%) Yes	19 (5%)	17 (10%)	2 (1%)
median-range	750ml (250-1500ml)	750ml (250-1500ml)	500ml (250-750ml)
During the dying phase			
Orally			
N (%) Yes	152 (41%)	66 (40%)	86 (42%)
median-range	250ml (25-1650ml)	250ml (25-1650ml)	220ml (27-1038m)
IV			
N (%) Yes	125 (34%)	121 (74%)	4 (2%)
median-range	179ml (6-1500ml)	179ml (6-1500ml)	297ml (31-719ml)
Tube			
N (%) Yes	12 (3%)	9 (6%)	3 (1%)
median-range	21ml (4-107ml)	31ml (5-107ml)	9ml (4-11ml)

Fluid intake

Patients' total fluid intake decreased during the last phase of life (table 1). During the week before the start of the CPD, 78% of patients had a total fluid intake of ≥ 500 ml/day, which decreased to 45% of patients during the last day before the start of the CPD and 15% during the dying phase. Fluid intake mainly involved oral intake, which decreased during the last days of life. During the week before the start of the CPD, 81% of patients had an oral intake of fluid, which decreased to 69% of patients during the last day before the start of the CPD

and 41% during the dying phase. Twenty-four percent of patients had IV hydration during the week before the start of the CPD, 25% during the last day before the start and 34% during the dying phase. IV hydration was predominantly prescribed in the hospital. Intake via a feeding tube involved 6% of patients during the week before the start of the CPD, 5% during the last day before the dying phase, and 3% during the dying phase. Detailed information concerning fluid intake per care setting is described in table 2.

Prevalence of death rattle and terminal restlessness

Figure 1 shows the percentages of patients with death rattle or terminal restlessness per period of 4 hours before death. Overall, death rattle was reported at least once in 40% (n=149) of patients during the dying phase, and in 35% (n=130) of patients during the last 24 hours of life. Death rattle scores of ≥2 were often reported more than once; 62% of patients with death rattle had 2 or more death rattle scores of ≥2 and 35% of these patients had 3 or more of such episodes. The prevalence of death rattle increased with death coming nearer. Terminal restlessness was reported at least once in 26% of patients (n=96) during the dying phase and in 13% (n=49) of patients during the last 24 hours of life. For most patients with terminal restlessness (61%), terminal restlessness was only reported once; 19% had terminal restlessness at ≥3 measurements. Terminal restlessness occurred almost evenly throughout the dying phase.

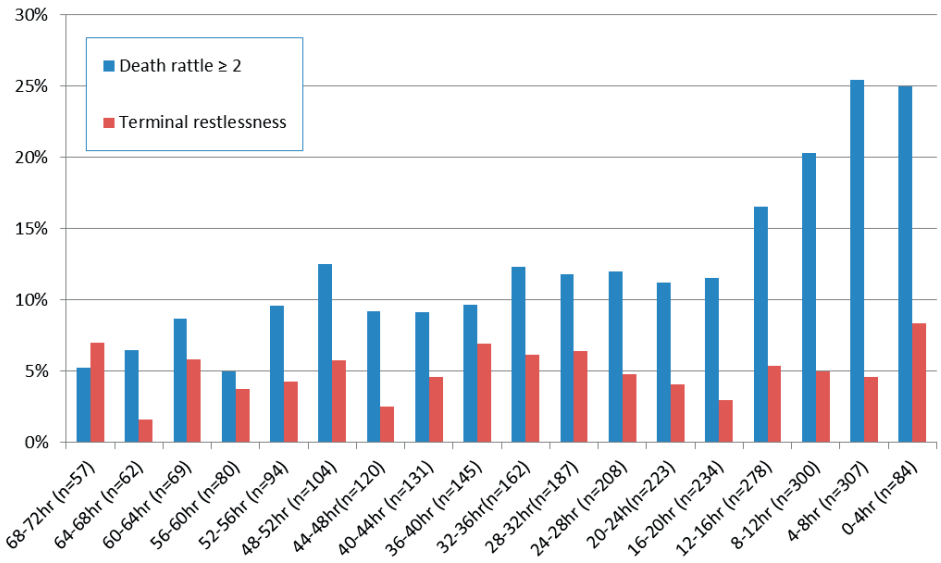

Figure 2. Percentage of patients with death rattle or terminal restlessness score per four-hourly measurement during the last 72 hours of life

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
		N (%)		N (%)		N (%)		N (%)	
Gender			0.361		0.323		0.575		0.342
Male	181	77 (43%)		51 (28%)		66 (36%)		27 (15%)	
Female	190	72 (38%)		45 (24%)		64 (34%)		22 (21%)	
Age (years)			0.51		0.12		0.084		0.159
<65	102	44 (43%)		33 (32%)		40 (39%)		19 (19%)	
65-75	116	36 (31%)		28 (24%)		31 (27%)		12 (10%)	
>75	152	68 (45%)		35 (23%		58 (38%)		18 (12%)	
Diagnosis			0.830		0.643		0.970		0.640
Cancer	289	118 (41%)		76 (26%)		102 (35%)		36 (12%)	
Non-cancer	76	30 (39%)		18 (24%)		27 (36%)		11 (14%)	
Place of death			0.977		0.117		0.748		0.679
Hospital	164	66 (40%)		49 (30%)		56 (34%)		23 (14%)	
Hospice	207	83 (40%)		47 (23%)		74 (36%)		26 (13%)	
Duration of the dying phase (hours)			0.458		**0.003**		0.416		0.138
< 24	169	62 (37%)		30 (18%)		62 (37%)		16 (9%)	
24–48	104	45 (43%)		31 (30%)		39 (38%)		18 (17%)	
>48	98	42 (43%)		35 (36%)		29 (30%)		15 (15%)	
Level of consciousness at the start of the CPD			0.153		**0.001**		0.350		0.159
Conscious	112	39 (35%)		34 (30%)		34 (30%)		19 (17%)	

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371) (continued)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
Semi- conscious	175	78 (45%)		53 (30%		67 (38%)		23 (13%)	
Unconscious	80	29 (36%)		8 (10%)		26 (32%)		6 (8%)	
Opioid use during the last day before the start of the CPD			0.820*		0.221*		0.378*		0.233*
1st quartile (<29 mg/24h)	67	26 (39%)		16 (24%)		23 (34%)		10 (15%)	
2nd quartile (29 mg - 74 mg/24h)	64	26 (41%)		20 (31%)		25 (39%)		11 (17%)	
3rd quartile (75 mg – 179 mg/24h)	69	23 (33%)		15 (22%)		22 (32%)		7 (10%)	
4th quartile (≥180 mg/24h)	72	34 (47%)		23 (32%)		29 (40%)		13 (18%)	
Opioid use during the period 48-24 hrs before death			NA		NA		0.332*		0.132*
1st quartile (<8 mg/24h)	91	NA		NA		25 (27%)		7 (8%)	
2nd quartile (8 mg - 57 mg/24h)	94	NA		NA		37 (39%)		14 (15%)	
3rd quartile (58 mg – 143mg/24h)	91	NA		NA		29 (32%)		11 (12%)	
4th quartile (≥144 mg/24h)	95	NA		NA		39 (41%)		17 (18%)	
Total daily fluid intake during the week before the start of the CPD			0.186*		0.074*		0.324*		0.265*
0-499ml per day	74	26 (35%)		14 (19%)		23 (31%)		7 (9%)	
500-999ml per day	117	47 (40%)		33 (28%)		42 (36%)		16 (14%)	
≥1000ml per day	144	64 (44%)		45 (31%)		55 (38%)		22 (15%)	
Total daily fluid intake during the last day before the start of the CPD			0.065*		0.384		0.435*		0.398*
0-499ml per day	187	70 (37%)		46 (25%)		65 (35%)		22 (12%)	
500-999ml per day	70	28 (40%)		24 (34%)		24 (34%)		11 (16%)	
≥1000ml per day	81	41 (51%)		22 (27%)		33 (41%)		12 (15%)	

Table 3. Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics (n=371) (continued)

	N	Symptom present somewhere during the dying phase				Symptom present during the last 24h of life			
		Death rattle score ≥2 (n=149)	P Value	Terminal restlessness (n=96)	P Value	Death rattle score ≥2 (n=130)	P Value	Terminal restlessness (n=49)	P Value
Total daily fluid intake during the period 48-24 hours before death			NA		NA		0.130*		**0.049***
0-249ml per day	190	NA		NA		74 (39%)		19 (10%)	
250-499ml per day	44	NA		NA		15 (34%)		8 (18%)	
≥500ml per day	121	NA		NA		37 (31%)		21 (17%)	

Statistics: Chi-Square; *Mann-Whitney
NA = not applicable

Associations between death rattle or terminal restlessness with fluid intake and other patient characteristics

No significant association between death rattle and the amount of fluid intake was found (Table 3). A higher amount of fluid intake during the week and day before the start of the CPD tended to be associated with an increased occurrence of death rattle. Terminal restlessness was not associated with a lower amount of fluid intake during the days before dying. Terminal restlessness during the last 24 hours of life was statistically significant associated with a higher amount of fluid during the time period 48-25 hours before death (p=0.049). Patients' level of consciousness at the start of the dying phase and the duration of the dying phase were also associated with terminal restlessness. Being conscious or semi-conscious at the start of the dying phase was associated with a higher occurrence of terminal restlessness during the dying phase (p=0.004). A longer duration of the dying phase was also associated with a higher occurrence of terminal restlessness (p=0.003).

DISCUSSION

We found no significant association between the amount of fluid intake and the occurrence of death rattle. We did not find an association between a lower amount of fluid intake and terminal restlessness either. Terminal restlessness during the last 24 hours of life was however associated with a higher amount of fluid intake during the time period 48-25 hours before death.

Three previous studies have assessed death rattle occurrence and its association with AH7 9 14. Morita et al.14 performed a multicentre, prospective, observational study of patients dying from cancer. Patients were divided in two groups: those who received 1 liter or more of AH per day both 1 week and 3 weeks before death (hydration group n=59) and those who did not (non-hydration group n = 167). During the last 3 weeks of life, 44% of patients in the hydration group and 46% of patients in the non-hydration group were recorded as presenting with death rattle (p=0.79). Yamaguchi et al.9 also performed a prospective observational study of patients dying from cancer. A comparison was made between patients who received more than 1liter of AH a day (large-volume hydration group n=76) and patients who received less than 1 liter a day (small-volume hydration group n=75). However, this classification was made on the basis of their intake of AH at inclusion in the study, not taking into account any change in fluid intake closer to death. In total, 43% of patients were recorded as presenting with death rattle during 48 hours before death, 51% in the large-volume group and 35% in the small-volume group (p=0.07). Fritzson et al.[7] performed a medical record review in which he studied patients who died in hospital and compared patients who had received parenteral fluid (PF group) to matched control patients who had not received parenteral fluid (non-PF group). During the last week of life 60% of all patients presented with death rattle, 63% in the PF group and 50% in the non-PF group (p=0.07). During the last 24 hours of life 46% of

all patients presented with death rattle, 50% in the PF group and 33% in the non-PF-group (p=0.02). Morita[14] and Fritzson[7] both reported on an AH intake of 1liter during the last 24 hours before death, not taking into account any oral intake. These intakes of AH are high compared to the median fluid intake in our study; 334 ml during the day preceding the last 24 hours.

We did not find an association between a lower amount of fluid intake during the days before dying and the occurrence of terminal restlessness. Terminal restlessness during the last 24 hours of life was however associated with a higher amount of fluid during the time period 48-25 hours before death. Previous studies on the relation between fluid intake and occurrence of terminal restlessness or delirium showed diverse results. Morita et al.[14] failed to show a difference in delirium occurrence between hydrated and non-hydrated patients with a prevalence of 12% in the hydration group and 13% in the non-hydration group (= 0.80). Bruera et al.[11] performed a randomized controlled trial in 129 patients with advanced cancer. Patients were divided in two groups: those who received 1 liter of AH per day for the duration of a week (hydration group), and those who received 110 ml of AH per day (placebo group). No differences were found between the two groups in the occurrence of delirium. Yamaguchi et al.[9] found a higher occurrence of delirium in patients who received less than 1 liter of fluid a day compared to patients who received more than 1 liter (17% vs 5%, p=0.01) and proposed hydration as an intervention to treat delirium. Our finding of an association between more fluid intake and more terminal restlessness is in line with the study by Fritszon et al.[7] who also found a higher occurrence of terminal restlessness in patients receiving AH during the last 24 hours of life as compared to patients without AH.

This study has some limitations. Firstly, the optimal design to study the effects of fluid intake would be a randomized controlled trial, which would however pose ethical challenges. We conducted a prospective observational study to explore variations in fluid intake in daily practice. Secondly, the patient's oral intake was based on nurses' estimation. It would have been more reliable if we had used a fluid balance measure. However a fluid balance measure would lead to medicalizing the dying phase and is therefore not a common practice at the end of life. Thirdly, at the start of this study no instrument to measure terminal restlessness was available. Because of the close connection between restlessness and calmness, we decided to use the calmness scale of the Vancouver Interaction and Calmness Scale. We did not use any other instrument to validate the calmness scale and it is possible that patients were misclassified. However, the prevalence reported in this study is in line with other studies focusing on terminal restlessness and delirium at the end of life. Fourthly, we collected information on fluid intake at three moments in time; the week before the start of the CPD, the day before the start of the CPD and, 4 hourly, during the dying phase. Information on symptom occurrence was measured, 4 hourly, during the dying phase. Relating the total fluid intake during the dying phase to symptom occurrence during the dying phase could mean relating a symptom occurring at the start of the dying phase to an average level of

fluid intake based on the entire dying phase. Therefore we calculated a separate variable concerning the fluid intake during the time period 48-25 hours before death. Whereas terminal restlessness occurred almost evenly throughout the dying phase and often only once, it is possible that patients in the non-symptom group during the last 24 hours of life actually presented with terminal restlessness before the last 24 hours of life but were successfully treated (i.e. sedated). We found no evidence that patients with terminal restlessness were more often sedated compared to patients who were not terminal restless (p=0.23, not in table). Fifthly, the high percentage of missings for the measurement period 4-0 hours before death could mean that we over- or underestimated the occurrence of death rattle and terminal restlessness during that 4 hourly period. From daily practice we know that completing the measurement for this time period is often forgotten by nurses because completion is required after the patient has died. However, the terminal restlessness percentage is in line with what we would expect based on the other measurements and daily practice. Looking at the increase in death rattle occurrence during the 4 previous measurements, it is possible that the actual percentage for death rattle would have been higher. Consensus about the natural course of death rattle, whether it increases or decreases closer to death, is still lacking. Kass and Ellershaw suggest that the prevalence of death rattle typically increases when death approaches[26]. Yet, Heisler et al.[27] performed a placebo controlled trial and found an decrease of death rattle scores over time in the placebo group. Sixthly, we did not make a distinction between types of opioids and added up opioids with different opioid metabolisms. It is possible that by combining opioids we lost the ability to show associations between specific opioid use and occurrence of symptoms on the one hand and/or specific opioid use and level of hydration of the other hand.

In conclusion, we found that a higher amount of fluid intake (i.e. possible over-hydration), preceding and during the dying phase, was not associated with the occurrence of death rattle. Further, a lower amount of fluid intake (i.e. possible under-hydration), preceding and during the dying phase, was not associated with the occurrence of terminal restlessness. Caution with fluid intake to prevent development of death rattle does not seem to be necessary. Our study suggests that a higher amount of fluid intake during the period 48-25 hours before death may be related to occurrence of terminal restlessness during the last 24 hours of life. Actively providing dying patients with artificial fluid therefore does not seem to be beneficial.

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APPENDIX

Variables used in this study

Part 1 of the CPD, *reflecting the patient's situation at the start of the dying phase*

- Diagnosis (cancer, non-cancer)
- Gender (male, female)
- Date of birth
- Date and time of the start of the CPD
- Level of consciousness (conscious, semi-conscious, unconscious)
- Prevalence of restlessness (yes, no)
- Prevalence of confusion (yes, no)
- Prevalence of respiratory tract secretions (yes, no)

Questions added to part 1 of the CPD specifically for this study

- Has the patient used opioids in the last 24 hours? (yes/no)
  - Indicate route (transdermal, oral, rectal, oral, nasal), type (morphine,...) and the total dose during the past 24 hours
- Total fluid intake during the week preceding the recognition of the dying phase
  - Oral intake (1 cup is approximately 250 ml)
  - None
  - Sibs
  - Between 1-4 cups/ day
  - More than 4 cups/ day
- Intravenous infusion
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Feeding tube
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Total fluid intake during the last 24 hours preceding the recognition of the dying phase
  - Oral intake (1 cup is approximately 250 ml)
  - None

  - Sibs
  - Between 1-4 cups/ day
  - More than 4 cups/ day
- Intravenous infusion
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more
- Feeding tube
  - None
  - Less than 0,5 l/day
  - 0,5-1 l/day
  - 1-1,5 l/day
  - 1,5 l/day and more

Part 2 of the CPD, *reflecting the patient's situation from the start of the dying phase until death*

Questions added to part 2 of the CPD specifically for this study

- Total fluid intake, per four hourly intervals, until death
  - Oral intake (1 cup is approximately 250 ml)
    - None
    - Sibs
    - 1 cup
    - More than 1 cup
  - Intravenous infusion
    - None
    - Less than 0,5 l/day
    - 0,5-1 l/day
    - 1-1,5 l/day
    - 1,5 l/day and more
  - Feeding tube
    - None
    - Less than 0,5 l/day
    - 0,5-1 l/day
    - 1-1,5 l/day
    - 1,5 l/day and more
- Has the patient used opioids in the last 4 hours? (yes/no)

  - Indicate route (transdermal, oral, rectal, oral, nasal), type (morphine,...) and the total dose during the past 24 hours
- Has the patient had death rattle in the last 4 hours? (yes/no)
  - 0, inaudible
  - 1, audible only very close to the patient
  - 2, clearly audible at the end of the bed, in a quiet room
  - 3, clearly audible at the door of the room (about 20 feet / 10 meter), in a quiet room.
- Please indicate to what extend you agree (strongly agree, agree, mildly agree, mildly disagree, disagree, strongly disagree) with the following statements
  - 1, patient appears calm
  - 2, patient appears restless
  - 3, patient appears distressed
  - 4, patient is moving around uneasily in bed
  - 5, patient is pulling at lines/tubes.

Part 3 of the CPD, *reflecting the situation after death*

- Date and time of death

Questions added to part 3 of the CPD specifically for this study

- Did the patient receive palliative sedation (yes/no)