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Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life
The SILENCE Randomized Clinical Trial

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IMPORTANCE *Death rattle*, defined as noisy breathing caused by the presence of mucus in the respiratory tract, is relatively common among dying patients. Although clinical guidelines recommend anticholinergic drugs to reduce the death rattle after nonpharmacological measures fail, evidence regarding their efficacy is lacking. Given that anticholinergics only decrease mucus production, it is unknown whether prophylactic application may be more appropriate.

OBJECTIVE To determine whether administration of prophylactic scopolamine butylbromide reduces the death rattle.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized, double-blind, placebo-controlled trial was performed in 6 hospices in the Netherlands. Patients with a life expectancy of 3 or more days who were admitted to the participating hospices were asked to give advance informed consent from April 10, 2017, through December 31, 2019. When the dying phase was recognized, patients fulfilling the eligibility criteria were randomized. Of the 229 patients who provided advance informed consent, 162 were ultimately randomized. The date of final follow-up was January 31, 2020.

INTERVENTIONS Administration of subcutaneous scopolamine butylbromide, 20 mg four times a day (n = 79), or placebo (n = 78).

MAIN OUTCOMES AND MEASURES The primary outcome was the occurrence of a grade 2 or higher death rattle as defined by Back (range, 0-3; 0, no rattle; 3, rattle audible standing in the door opening) measured at 2 consecutive time points with a 4-hour interval. Secondary outcomes included the time between recognizing the dying phase and the onset of a death rattle and anticholinergic adverse events.

RESULTS Among 162 patients who were randomized, 157 patients (97%; median age, 76 years [IQR, 66-84 years]; 56% women) were included in the primary analyses. A death rattle occurred in 10 patients (13%) in the scopolamine group compared with 21 patients (27%) in the placebo group (difference, 14%; 95% CI, 2%-27%, *P* = .02). Regarding secondary outcomes, an analysis of the time to death rattle yielded a subdistribution hazard ratio (HR) of 0.44 (95% CI, 0.20-0.92; *P* = .03; cumulative incidence at 48 hours: 8% in the scopolamine group vs 17% in the placebo group). In the scopolamine vs placebo groups, restlessness occurred in 22 of 79 patients (28%) vs 18 of 78 (23%), dry mouth in 8 of 79 (10%) vs 12 of 78 (15%), and urinary retention in 6 of 26 (23%) vs 3 of 18 (17%), respectively.

CONCLUSIONS AND RELEVANCE Among patients near the end of life, prophylactic subcutaneous scopolamine butylbromide, compared with placebo, significantly reduced the occurrence of the death rattle.

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Section Editor: Christopher Seymour, MD, Associate Editor, *JAMA* (christopher.seymour@jamanetwork.org).

Death rattle, defined as "noisy breathing caused by the presence of mucus in the upper respiratory tract" is relatively common in dying patients.[1,2] A systematic review from 2014 found that the prevalence of the death rattle ranged from 12% to 92%.[1] Although suggested that patients are not affected by the death rattle due to their reduced consciousness in this final phase of life,[3] the actual effect on the patient experience is unknown. Patients' relatives and other observers can find the rattling sounds stressful and disturbing because as they may be concerned that the patient is experiencing harm or choking.[1,4,5] The management of the death rattle generally consists of repositioning the patient to reduce potential burden for the patient, as well as informing and attempting to reassure relatives and other observers.[5] However, information alone may not be sufficient to improve the relatives and other observers' experience.[6]

In cases in which nonpharmacological measures fail, several guidelines recommend the subsequent use of anticholinergic drugs to diminish the death rattle.[7,8] However, 2 placebo-controlled randomized clinical trials (RCTs) found no evidence supporting a beneficial effect of anticholinergic treatment.[9,10]

Anticholinergics decrease the production of mucus and therefore do not affect existing mucus; thus administering an anticholinergic drug after the onset of a death rattle may be less effective[11] than prophylactic use (ie, before its onset).[10] In 2018, a randomized trial, in which providing scopolamine butylbromide prophylactically from the start of the dying phase was compared with providing this medication when the death rattle occurred, found favorable results in patients who received scopolamine butylbromide prophylactically.[12] However, this study was not blinded. To further investigate whether prophylactic scopolamine butylbromide could reduce the death rattle, the SILENCE (Scopolamine Butylbromide Given Prophylactically for Death Rattle) study was conducted.

Methods

Trial Design

This study was a randomized, double-blind, placebo-controlled, multicenter clinical trial designed to study the efficacy of prophylactic scopolamine butylbromide in the prevention of a death rattle in dying patients. The original protocol is presented in Supplement 1 and the statistical analysis plan, in Supplement 2. The study protocol has been published.[13]

The study began in April 2017 and initially included 4 inpatient hospice facilities. Because of an insufficient recruitment rate and the withdrawal of one of these sites (eTable 1 in Supplement 3), the study protocol was amended in August 2018 and September 2018 in order to add 2 more hospice facilities. The study ended in December 2019 with a final follow-up date of January 31, 2020. The trial was approved by the Medical Ethical Research Committee of the Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands. Patients provided advance written informed consent to participate and were aware that their participation in the study would begin at the recognition of their dying phase (ie, in the predicted last days of life).

Key Points

Question For patients near the end of life, does prophylactic administration of subcutaneous scopolamine butylbromide reduce the occurrence of the death rattle (defined as noisy breathing caused by the presence of mucus in the upper respiratory tract)?

Findings In this randomized clinical trial that included 162 patients, a death rattle was observed at 2 consecutive time points 4 hours apart in 13% of patients in the scopolamine butylbromide group and in 27% of patients in the placebo group, a statistically significant difference.

Meaning Among patients near the end of life, prophylactic subcutaneous scopolamine butylbromide significantly reduced the occurrence of the death rattle.

Patient Population

Adults who were admitted to a participating hospice could be included when they met the following inclusion criteria: the patient had a life expectancy of at least 3 days; the patient was aware that the hospice admission would last until death; and the patient was able to understand the information provided regarding the study. Patients were excluded if they had a tracheostomy or tracheal cannula; used a systemic anticholinergic drug or octreotide; or had an active respiratory infection. At the recognition of the dying phase, the patients were re-assessed for their eligibility based on the following criteria: they did not have an active respiratory infection; they did not use systemic anticholinergic drugs; and they did not have any death rattle.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to receive either scopolamine butylbromide or placebo in batches with consecutively numbered—but otherwise identical—boxes (Figure 1). The boxes were prepared by the central pharmacist at the Erasmus Medical Center using a randomization list that was provided by an independent statistician. Each box contained 16 identical ampoules of either scopolamine butylbromide (20 mg in 1 mL) or placebo (physiological saline 1 mL), which was sufficient for treating 1 patient for 4 days. If a patient's dying phase lasted longer than 4 days, an extra box from a separate batch was used; in this situation, the central pharmacist provided the number of the extra box that was to be used. During the study, all patients, relatives, other observers, health care professionals, and researchers were blinded to the study group assignment. Randomization was stratified by each hospice with a variable block size of 2 to 4 patients using R version 3.2.3.

Trial Interventions

When the health care professional recognized that a participating, eligible patient had entered the dying phase, either 20 mg of scopolamine butylbromide or placebo was administered subcutaneously 4 times a day using an indwelling subcutaneous catheter. The dying phase starts when death becomes imminent according to the clinical judgment of the multidisciplinary team taking into account a number of signs:

Figure 1. Study Flow of the Scopolamine Butylbromide Given Prophylactically for Death Rattle (SILENCE) Study
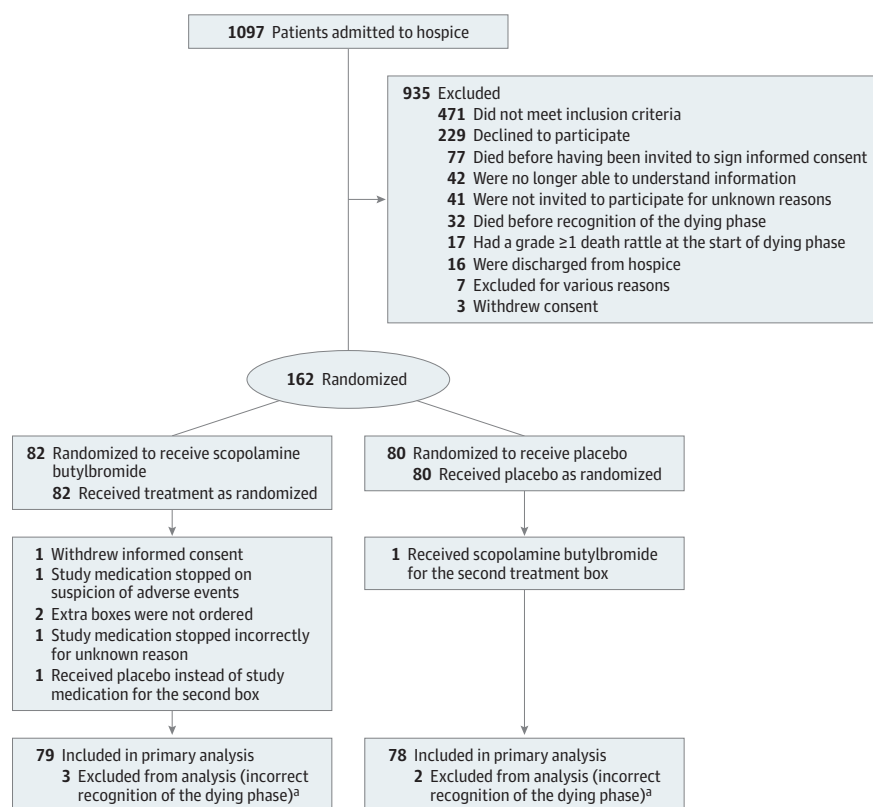
^a Included in post hoc analysis.

the patient is bedbound, is only able to take sips of fluid, is no longer able to swallow and take oral medication, and appears to be semicomatose.[14] The medication continued until death or until the occurrence of grade 2 or higher death rattle (as defined by Back et al[15]) was measured at 2 consecutive time points at an interval of 4 hours apart (the end point of the study for this patient). When this point was reached, the study medication failed and the patient received care as usual, which could include the administration of open-label anticholinergics.

Patients who completed 2 boxes of study medication (ie, 32 doses) were withdrawn from the study because it was assumed that the patient had not entered the dying phase.

Upon recognizing the dying phase, the Care Program for the Dying (CPD) was used. The CPD is a digital, structured template for providing care in the dying phase.[16] Every 4 hours until death, 13 physical, psychological, social, and spiritual goals of care are evaluated and documented as either achieved (eg, symptom controlled) or not achieved (eg, symptom not controlled). For this study, the template was expanded with 2 scales, namely the death rattle scale reported by Back et al[15] and the Vancouver Interaction and Calmness Scale[17] (VICS) for restlessness.

The primary researcher (H.J.v.E.) trained the health care professionals on site in implementing the study protocol, use of rating scales, and registration of patients. Furthermore, the procedures for rating and registration in the CPD were described in a standard operating procedure in an effort to reduce internurse variability.

Outcomes

The primary end point was the occurrence of a grade 2 or higher death rattle based on the scale published by Back et al[15] measured at 2 consecutive time points at an interval of 4 hours. The scale consists of 4 categories: 0, no rattle; 1, audible close to the patient; 2, audible standing at the end of the bed; and 3, audible standing in the door opening.

Secondary end points included the time between recognition of the dying phase and the occurrence of a death rattle (in hours) and the occurrence of prespecified, adverse events potentially related to the use of an anticholinergic drug (eg, restlessness, dry mouth, or urinary retention). Restlessness, dry mouth, and urinary retention were considered to have occurred if the corresponding goals in the CPD were registered at least once as not achieved. Dry mouth was registered as not achieved when it became necessary to provide oral care more frequent than the standard care which was given every 4 hours. Restlessness was also assessed using the calmness subscale of the VICS[17] that consists of 5 questions (patient appears calm, patient appears restless, patient appears distressed, patient is moving around uneasily in bed, and patient is pulling at lines or tubes) scored on a 6-point Likert scale (range, strongly agree to strongly disagree); interrater reliability 0.89 and internal consistency 0.95; a positive response scored as (strongly) agree to at least 2 of the 5 questions on this scale at 2 consecutive time points at an interval of 4 hours was considered to represent restlessness as an adverse event.

Exploratory end points included the time between recognition of the dying phase and death (in hours), the use of any other medications, and the use of sedatives. The occurrence of concurrent symptoms (eg, pain, dyspnea, nausea, or vomiting) that could interfere with the evaluation of the primary outcome or adverse events was also measured. These symptoms were considered to have occurred if the corresponding goals in the CPD were registered at least once as not achieved.

Prespecified secondary end points, which are not reported in this article, were the quality of life during the last 3 days of life and the quality of dying according to the bedside nurse, assessed immediately after death; the quality of life during the last 3 days of life and quality of dying according to relatives, bereavement of relatives, and the experience of relatives with the patient's participation in a randomized clinical trial, assessed 3 months after death.

Sample Size

In a previous study involving 400 patients, 39% developed a death rattle classified as grade 2 or higher.[18] Based on the consensus opinion of the investigators who designed the study, a relative reduction of 50% was considered clinically relevant. Our a priori aim therefore was to reduce the occurrence of death rattle to 19%. Given a 2-sided significance level of 5% and 80% power, a total of 180 patients was required based on a continuity-corrected χ^2 test. Taking into account that up to 10% of patients who give informed consent might not be able to be randomized (for example due to sudden death or the onset of exclusion criteria), a total of 200 patients was required.

Statistical Analysis

Patients were analyzed according to their randomization group. Patients who were determined not to be in the dying phase after randomization were excluded from the prespecified analyses. If a patient or the family withdrew informed consent during the study, the data collected up until the time of withdrawal were included in the analyses; if a death rattle or other concurrent symptoms and adverse events were not documented prior to the patient's withdrawal, they were considered to not have occurred in the analyses of occurrence rates. Missing data were not imputed.

For the primary outcome (ie, the occurrence of a death rattle), the 2 groups were compared using the χ^2 test. Post hoc, mixed logistic regression modeling was used with site as a random effect to test whether there was a site effect. A post hoc sensitivity analysis was performed for the primary end point in which the patients who were determined not to be in the dying phase after randomization were included and imputed as treatment failures.

For the secondary outcomes, the time between recognition of the dying phase and the onset of death rattle (measured in hours) was analyzed using the proportional hazards model for the subdistribution (results denoted by the subdistributional hazard ratio [HR] as described by Fine and Gray[19] with death as a competing risk, and is illustrated using the cumulative incidence function. Given the possibility that a patient who had a death rattle at only 1 time point could have died or withdrawn from the trial before death rattle could be observed during a consecutive measurement, sensitivity analyses were performed for the above mentioned analyses, with the occurrence of a grade 2 or higher death rattle at 1 measurement point but not followed by improvement (eg, due to death or withdrawal) as the outcome. The occurrence of prespecified adverse events were described by treatment group, while the time between recognition of the dying phase and the onset of each symptom or adverse event was analyzed using a proportional hazards model for the subdistribution,[19] with the death rattle and death as competing risks.

For the exploratory outcomes, the time between recognition of the dying phase and death is reported using a Kaplan-Meier survival plot, and the difference between treatment groups was analyzed using Cox regression. The use of other medication and the use of sedatives are described for each treatment group. The occurrence of pain, dyspnea, nausea, or vomiting is described by treatment group, while the time between recognition of the dying phase and the onset of each symptom or adverse event was analyzed using a proportional hazards model for the subdistribution,[19] with the death rattle and death as competing risks. Post hoc, the occurrence of a death rattle in the placebo-treated subgroups of patients with lung cancer, COPD as a comorbidity, and a recent history of smoking were assessed.

For all time-to-event analyses, the proportionality assumption was checked by means of Schoenfeld residuals and by using cumulative hazard plots. No violations of the assumption were found. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All reported *P* values are based on 2-sided testing and differences were considered significant at *P* < .05. All analyses were performed using Stata, version 15.1 (StataCorp).

Results

Trial Flow and Baseline Characteristics of Participants

From April 10, 2017, through December 31, 2019, 1097 patients were admitted to the participating hospices, of whom 229 patients provided advance informed consent (Figure 1). Of these 229 patients, 162 were randomized and 157 patients were ultimately eligible for the final analyses; 79 of these patients received scopolamine butylbromide and 78 received placebo. The baseline characteristics for the 2 treatment groups are presented in **Table 1**. Among all 157 patients, 86% had cancer as primary diagnosis. COPD and cardiovascular diseases were the most common comorbidities. In the respective scopolamine butylbromide and placebo groups 18% vs 35% had lung cancer, 10% vs 23% had COPD as comorbidity, and 14% vs 33% had smoked the previous year. Hospice A accounted for 73% of the participants. None of the patients who were randomized received any form of medical aid in dying. There were no missing data for the primary end point or reported secondary end points.

Primary Outcome

A significantly lower percentage of patients in the scopolamine butylbromide group developed a death rattle than did

Table 1. Baseline Characteristics of the Study Participants

Characteristic	No. (%) of patients	
	Scopolamine butylbromide group (n = 79)	Placebo group (n = 78)
Sex		
Men	36 (46)	33 (42)
Women	43 (54)	45 (58)
Age at admission to hospice, median (IQR), y	78 (69-86)	75 (64-83)
Primary diagnosis, No./total (%)		
Cancer	66 (84)	69/77 (89)
Lung	14 (18)	27/77 (35)
Gastrointestinal	13 (16)	13/77 (17)
Breast	10 (13)	4/77 (5)
Head and neck	3 (4)	3/77 (4)
Other	26 (33)	22/77 (28)
Not cancer	13 (16)	8/77 (10)
Cardiovascular disease	8 (10)	1/77 (1)
Chronic obstructive pulmonary disease	1 (1)	2/77 (3)
Cerebrovascular accident	1 (1)	2/77 (3)
Other	3 (4)	3/77 (4)
Comorbidity		
Cardiovascular disease	21 (27)	21 (27)
Diabetes	10 (13)	7 (9)
Chronic obstructive pulmonary disease	8 (10)	18 (23)
Cerebrovascular event	8 (10)	6 (8)
Dementia	0	1 (1)
Other	12 (15)	10 (13)
Smoked in the previous year	11 (14)	26 (33)
Urinary catheter in situ at the recognition of dying phase	50 (63)	56 (72)
Sedatives given at the recognition of the dying phase	15 (19)	16 (21)
Hospices		
A	55 (70)	59 (76)
B	13 (16)	9 (12)
C	6 (8)	7 (9)
D	4 (5)	2 (3)
E	1 (1)	0
F	0	1 (1)
Time between given consent and recognition of the dying phase, median (IQR), d	14 (12-25)	15 (11-21)

the placebo group (10 [13%] vs 21 [27%], respectively; difference, 14%; 95% CI, 2%-27%; *P* = .02; **Table 2**). The sensitivity analysis confirmed this result (Table 2). The site effect was not significant (intraclass correlation <0.001; eTable 2 in Supplement 3).

In the post hoc sensitivity analysis, in which the 5 patients who were ultimately not dying were included as treatment failures, the percentage of patients developing a death rattle in the scopolamine butylbromide group was significantly lower than in the placebo group (16% vs 29%; difference, 13%; 95% CI, 0.2%-26%; *P* = .05; Table 2).

Secondary Outcomes

The analysis of the time to death rattle revealed a significantly lower instantaneous risk of death rattle in the scopolamine butylbromide group, with a subdistribution HR of 0.44

(95% CI, 0.20-0.92; *P* = .03; cumulative incidence at 48 hours, 8% vs 17%) (Table 2 and **Figure 2**A). The sensitivity analyses confirmed this result (Table 2 and Figure 2B).

Restlessness in the scopolamine butylbromide group occurred in 22 of 79 patients (28%) according to CPD and in 7 of 79 (9%) according to VICS, dry mouth in 8 of 79 (10%), and urinary retention in 6 of 26 (23%). Restlessness in the placebo group occurred in 18 of 78 patients (23%) according to CPD and in 7 of 78 (9%) according to VICS, dry mouth in 12 of 78 (15%), and urinary retention in 3 of 18 (17%; Table 2). The time to event analyses for the prespecified adverse events are shown in Table 2.

Exploratory Outcomes

The dying phase was significantly longer in the scopolamine butylbromide group (median, 42.8 hours; IQR, 20.9-80.1 hours;

Table 2. Summary of the Primary, Secondary, and Exploratory Outcomes in the Study of Scopolamine Butylbromide for Death Rattle

| | No. (%) | | Differences between percentages (95% CI), %[a] | P value | Cumulative occurrence at 48 h[b] | | | |
	Scopolamine butylbromide (n = 79)	Placebo (n = 78)			Scopolamine butylbromide, %	Placebo, %	Subdistribution HR (95% CI)[c]	P value
Primary outcome								
Death rattle grade ≥2								
2 Time points	10 (13)	21 (27)	14 (2 to 27)	.02				
1 Time point not followed by improvement[d]	15 (19)	29 (37)	18 (4 to 32)	.01				
Secondary outcomes								
Time from the recognition of the dying phase to death rattle								
2 Time points					8	17	0.44 (0.20 to 0.92)	.03
1 Time point without improvement[d]					8	22	0.41 (0.22 to 0.78)	.006
Adverse events								
Restlessness								
CPD[e]	22 (28)	18 (23)	–5 (–18 to 9)		23	19	1.25 (0.67 to 2.32)	.48
VICS[f]	7 (9)	7 (9)	0 (–9 to 9)		7	7	0.99 (0.35 to 2.81)	.98
Dry mouth[g]	8 (10)	12 (15)	5 (–5 to 16)		8	12	0.65 (0.27 to 1.57)	.34
Urinary retention[h]	6/26 (23)	3/18 (17)	–6 (–30 to 17)		20	15	1.45 (0.37 to 5.69)	.60
Exploratory outcomes								
Time from the recognition of the dying phase to death, median IQR, h	42.8 (20.9 to 80.1)	29.5 (13.5 to 54.1)	–13.3 (–17.4 to –6.4)[i]	.04	56	69	0.71 (0.52 to 0.98)[j]	.04
Use of medication								
Opioids	78 (99)	77 (99)	0 (–4 to 3)		NC	NC		
Midazolam	68 (86)	68 (87)	1 (–10 to 12)		NC	NC		
Haloperidol	31 (39)	25 (32)	–7 (22 to 8)		NC	NC		
Sedatives started during study treatment	20/63 (32)	18/62 (29)	–3 (–19 to 13)		NC	NC		
Symptoms								
Pain	42 (53)	33 (42)	–11 (–26 to 5)		45	37	1.27 (0.80 to 2.01)	.30
Dyspnea	15 (19)	14 (18)	–1 (–13 to 11)		15	15	1.04 (0.50 to 2.14)	.92
Nausea	6 (8)	4 (5)	–2 (–10 to 5)		6	4	1.50 (0.42 to 5.31)	.53
Vomiting	7 (9)	4 (5)	–4 (–12 to 4)		7	4	1.74 (0.51 to 5.98)	.38
Post hoc outcomes								
Death rattle grade ≥2								
2 Time points[k]	13 (16)	23 (29)	13 (0.2 to 26)	.05				
1 Time point not followed by improvement[d,k]	18 (22)	31 (39)	17 (3 to 31)	.02				

Abbreviation: NC, not computed; medication was registered as given.

[a] Differences in percentages computed as placebo minus scopolamine butylbromide.

[b] Cumulative occurrence is reported as an absolute measure of time to event outcomes as medians are not reached.

[c] Subdistribution hazard ratio (HR) with death as a competing risk.

[d] Sensitivity analysis.

[e] See the Methods section for the Care Programme for the Dying (CPD) for definitions as applied to this study.

[f] See the Methods section for the Calmness Subscale of the Vancouver

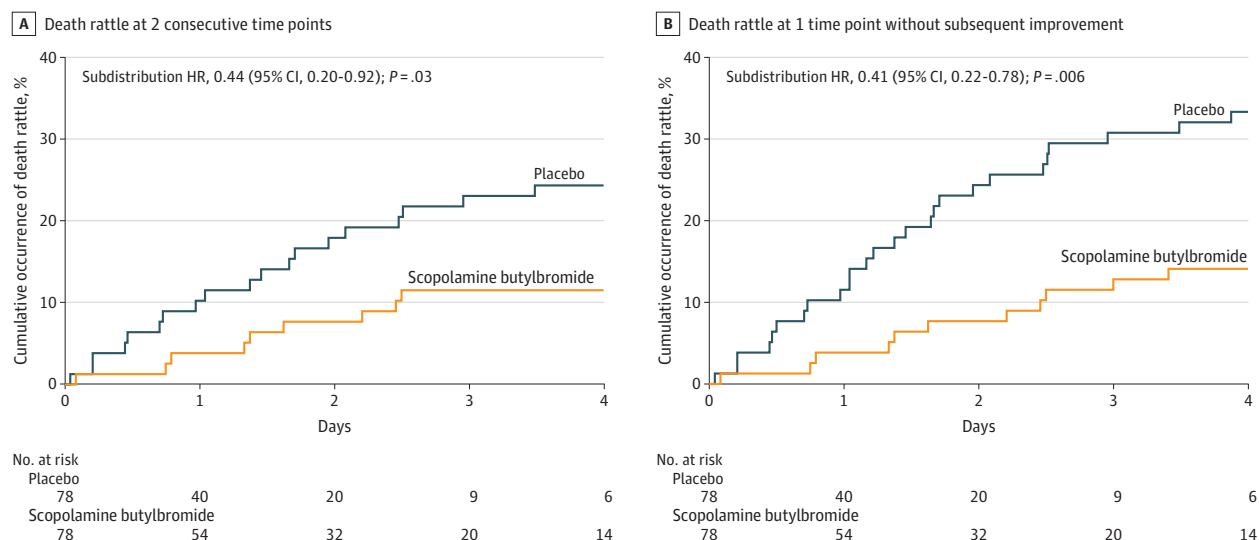Interaction and Calmness Scale (VICS) score range.

[g] Extra mouth care given in addition to standard care.

[h] Patients without a urinary catheter who developed urinary retention during the dying phase.

[i] Difference in median (IQR).

[j] HR.

[k] Primary outcome and sensitivity analysis of the 162 randomized patients with the 5 patients who were ultimately not dying included in the analysis and imputed as having a death rattle.

95% CI, 32.8-55.2) than in the placebo group (median, 29.5 hours; IQR, 21.1-41.7 hours; 95% CI, 21.1-41.7; *P* = .04) with an HR of 0.71 (95% CI, 0.52-0.98; *P* = .04; Table 2 and **Figure 3**). There was no significant difference in the use of opioids, haloperidol, and sedatives between the 2 groups. The 2 groups did not differ significantly with respect to instantaneous risk of the symptoms pain, dyspnea, nausea, and vomiting (Table 2).

The post hoc analysis showed that the occurrences of the death rattle in the placebo-treated subgroups of patients with lung cancer, COPD as a comorbidity, and a recent history of

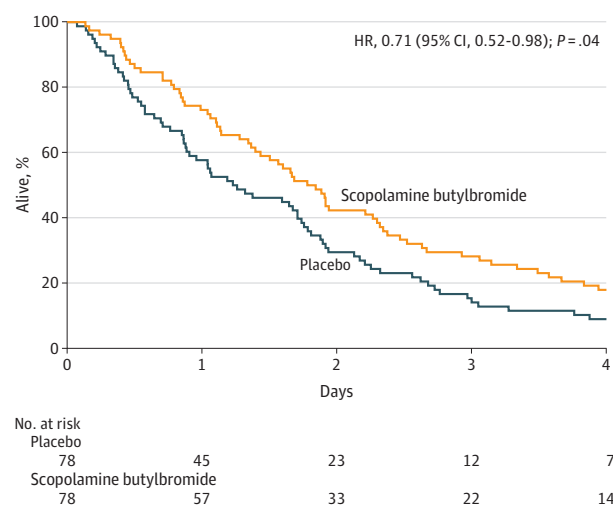Figure 2. Time Until the Death Rattle

A | Death rattle at 2 consecutive time points

Subdistribution HR, 0.44 (95% CI, 0.20-0.92); *P* = .03

B | Death rattle at 1 time point without subsequent improvement

Subdistribution HR, 0.41 (95% CI, 0.22-0.78); *P* = .006

No. at risk
| Placebo | 78 | 40 | 20 | 9 | 6 |
| Scopolamine butylbromide | 78 | 54 | 32 | 20 | 14 |

No. at risk
| Placebo | 78 | 40 | 20 | 9 | 6 |
| Scopolamine butylbromide | 78 | 54 | 32 | 20 | 14 |

A, The median observation time for the placebo group was 33.0 hours (IQR, 13.8-65.4 hours) and was 45.8 hours (IQR, 20.9-92.0 hours) for the scopolamine butylbromide group.

B, The median observation time for the placebo group was 41.0 hours (IQR,

13.8-72.0 hours) and was 43.5 hours (IQR, 20.9-94.6 hours) for the scopolamine butylbromide group.

HR indicates hazard ratio.

Figure 3. Time Until Death

HR, 0.71 (95% CI, 0.52-0.98); *P* = .04

No. at risk
| Placebo | 78 | 45 | 23 | 12 | 7 |
| Scopolamine butylbromide | 78 | 57 | 33 | 22 | 14 |

The median observation time for the placebo group was 29.9 hours (IQR, 13.3-54.1 hours). The median observation time for the scopolamine butylbromide group was 43.5 hours (IQR, 20.9-80.1 hours).

smoking were lower (11%, 17%, and 15%, respectively) than in the placebo group (eTable 3 in Supplement 3).

Discussion

This multicenter RCT found that the occurrence of the death rattle was significantly reduced by prophylactic subcutaneously administered scopolamine butylbromide. The prespeci-

fied adverse events were not substantially different between the 2 groups.

Based on the definition of the primary end point, a grade 2 or higher death rattle at 2 consecutive time points with an interval of 4 hours, it was found that 27% of the patients in the placebo group had a death rattle. However, when patients with a grade 2 or higher death rattle measured at a single time point prior to either their death or withdrawal were included, this percentage increased to 37%, which is consistent with published rates.[1,18]

This study found no clear evidence of increased rates of adverse events related to the use of anticholinergic drugs near the end of life. The symptoms of pain, dyspnea, nausea, and vomiting were not significantly different between the scopolamine butylbromide and placebo groups. This is generally similar to previous studies regarding the treatment of the death rattle using anticholinergics.[10,20] One exception was a placebo-controlled study involving hyoscine hydrobromide, which found a significant increase in pain in the hyoscine hydrobromide group.[9] Because pain can be difficult to assess in an unconscious patient, the authors may have interpreted restlessness or agitation as a sign of pain. In contrast, there were no substantial differences in pain or restlessness between the treatment groups in this study.

The study found that the placebo group included a higher percentage of patients with lung cancer as the primary disease, COPD as a comorbidity, and a history of smoking in the previous year than the patients in the scopolamine butylbromide group, even though the patients were randomly assigned to their respective treatment groups. In theory, this putative imbalance between the patient groups may have contributed to a higher occurrence of the death rattle in the

placebo group because patients with these conditions have an increased risk of respiratory problems with increased mucus production. However, a post hoc analysis revealed that the occurrence of the death rattle specifically in the placebo-treated patient subgroups with these conditions was lower than in the entire placebo group.

This study found that the dying phase was longer for the patients who received prophylactic scopolamine butylbromide than the patients who received placebo. Although this was an exploratory outcome, this finding is consistent with a previously reported randomized trial that found the mean duration of the dying phase was 45.2 hours among patients who received prophylactic hyoscine butylbromide compared to 41.1 hours among patients who received treatment after the onset of a death rattle.[12]

Performing an RCT with patients who are in the dying phase can be challenging.[21] However, this study shows that a randomized clinical trial is feasible in the context of daily hospice care. This process can be facilitated by using advance consent, appointing the hospice's physician as local researcher, and integrating outcome assessments into a digital, structured template used for monitoring patient care in the dying phase.[16] This study may serve as a model for future trials designed to obtain evidence regarding the treatment and/or relief of specific symptoms in the final phase of life.

Limitations

This study has several limitations. First, the final analysis included only 10% of all patients who were admitted to the participating hospice facilities during the study period. However, several factors likely contributed to this relatively low participation rate. Nearly half of all patients admitted to hospice were not eligible based on the study inclusion and exclusion criteria, largely because of an inability to understand the information and imminent death. Furthermore, some patients dropped out before they were able to make a decision regarding participation due to clinical decline, which underscores the high vulnerability of this study population. Approximately half of all patients who were able to make an informed decision regarding their participation in the study gave informed written consent. Nevertheless, it is unlikely that these patients had a different risk of experiencing a death rattle compared with the participating patients; thus, these results may be applicable to a larger patient population.

Second, these results may not necessarily apply to patients with a respiratory infection, for this was an exclusion criterion.

Third, some patients had already developed a death rattle at the time their health care professionals recognized that they had entered the dying phase. In this study, the dying phase was recognized based on a Dutch guideline regarding care in the dying phase,[8] which places the decision primarily in the hands of health care professionals. However, given that no validated tool currently exists for assessing the onset of the dying phase, a death rattle likely cannot be prevented in every dying patient.

Fourth, subcutaneous administration of medication might not be possible or desirable in all settings. The use of a patch to deliver medication might be a suitable alternative, although its effectiveness has not yet been studied to our knowledge.

Fifth, 114 of the 157 patients in this analysis (nearly 73%) were from one hospice; this is not unexpected because this hospice had the highest number of beds and participated throughout the entire length of the study.

Conclusions

Among patients near the end of life, prophylactic subcutaneous scopolamine butylbromide, compared with placebo, significantly reduced the occurrence of the death rattle.

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