Original Article

Hyoscine Butylbromide for the Management of Death Rattle: Sooner Rather Than Later

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Abstract

Context. Death rattle (DR) is a dramatic sign in the dying patient. Existing studies with anticholinergic agents are controversial, as this class of drugs has been commonly administered without considering the rationale of the mechanism of action. A meaningful use of these drugs may provide a better outcome.

Objectives. The aim of this study was to assess the efficacy of hyoscine butylbromide (HB), given prophylactically in comparison with HB administered once DR occurs.

Methods. Dying patients having a score of ≥3 in the Richmond Agitation-Sedation Scale—palliative version were included in the study. HB (60 mg/day) was given when DR occurred (Group 1) or as pre-emptive treatment (Group 2). The onset of DR (death rattle free time) and intensity of DR were recorded at intervals until death.

Results. Eighty-one and 51 patients were randomized to Group 1 and 2, respectively. Patients in Group 2 survived longer than those in Group 1 ($P < 0.05$). DR occurred in 49 (60.5%) and three patients (5.9%) in Group 1 and 2, respectively ($P = 0.001$). A significant difference in the number of patients reporting DR was found at intervals examined (30 minutes, one hour, and then every six hours until death [$P = 0.001$]). In Group 1 and 2, DR free time was 20.4 (20.5) and 27.3 hours (25.2), respectively ($P = 0.001$). In Group 1, the treatment was considered effective in 10 patients (20.4%) only, after a mean of 14.4 hours (SD 8.57).

Conclusion. The prophylactic use of HB is an efficient method to prevent DR, whereas the late administration produces a limited response, confirming data from traditional studies performed with anticholinergics. This could be considered a new paradigm to manage a difficult and dramatic sign, such as DR. J Pain Symptom Manage 2018;56:902–907. © *2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Cancer patient, palliative care, death rattle, dying process, anticholinergics, hyoscine butylbromide

Introduction

Death rattle (DR) is the noise produced by the oscillatory movements of secretions in the upper airways in association with the inspiratory and expiratory phases of respiration. The presentation of DR is frequent in the dying patient, with a prevalence ranging from 23% to 92%.[1–6] Such large differences are likely to be to variable assessment and settings. DR was strongly associated with death within two to three days among cancer patients[2,7] and more frequently occurs when the dying phase is prolonged.[1,4]

Airway secretions are produced by two sources, the salivary glands and the bronchial mucosa, each

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containing muscarinic receptors. Patients in semiconscious or deeply unconscious states are unable to swallow saliva or to cough up mucus from the trachea.[1,6] Loss of reflexes for coughing and swallowing is inevitable when the level of consciousness lowers, either spontaneously or when induced by palliative sedation.[5] Patients' perception is difficult to evaluate in terms of suffering because of the low level of consciousness, but relatives are often distressed in hearing the sound of DR, regardless of effective communication about DR and dispelling unwarranted fears.[8,9]

Anticholinergic drugs competitively antagonize acetylcholine at muscarinic receptors, leading to decreased production of secretions in the salivary, bronchial, and gastrointestinal tracts.[2,6] Despite these mechanisms, evidence-based literature does not support the standard use of antimuscarinic drugs in the treatment of DR.[10] In these studies, anticholinergic drugs have been administered to treat already formed noisy secretions rather than preventing their formation.[6] However, anticholinergic drugs are able only to reduce the formation of new secretions. It is likely in these circumstances that a pre-emptive treatment of DR could be more efficacious.[11] The aim of this study was to assess the efficacy of hyoscine butylbromide (HB), the most common anticholinergic drug used for DR, given prophylactically in the dying patient in a comparison with HB administered in patients who receive the same drug once DR occurs, according to previous studies. The primary outcome of this study was the number of patients reporting DR and effectiveness of treatments, according to intensity in DR.

Methods

This was an open-label, multicentric, prospective, and randomized trial. Patients were recruited in two hospices, in Latina and L'Aquila, Italy. Approval from the Regional Committee for Medical Research Ethics of the University of L'Aquila was obtained. The study was performed according to the rules of the Helsinki declaration. As the subject population consisted of patients with cognitive impairments or decreased consciousness, a surrogate informed consent was obtained from the caregiver. The study coordinators were responsible for ensuring that the caregivers were informed, written and orally, about the nature of the study. The study coordinator was available for answering questions that might arise and ascertained that caregivers had understood the content of the information, for example, that anonymous data would be stored for analyses later on. The study participation was on a voluntary basis, and patients could be withdrawn from the study whenever relatives required. Randomization was done by a closed-envelope system. An identity number was assigned to each patient automatically on study entry, regardless of whether the data were registered by computers. Each patient was given an access code for data entry on computers.

Design

Terminally ill patients, aged 18 years or more, considered to be close to death and presenting a reduction of the level of consciousness, either for a spontaneous neurological deterioration or because of palliative sedation, were eligible for the study. The threshold required to start the study was a value of ≤3 in the Richmond Agitation-Sedation Scale—palliative version (RASS-PAL).[12] Patients treated with other antimuscarinic medications within the current inpatient admission, patients already presenting DR, patients with clear secondary cause of rattle, called pseudo DR, including respiratory infection, food/fluid aspiration, or cardiac failure, were excluded.

Procedures

Patients with RASS-PAL of ≤3 were randomly assigned to one of two schedules of treatment (Fig. 1). Group 1 started HB only when DR developed with a score of ≥1 (see later); Group 2 received HB in a prophylactic perspective in the absence of DR. All patients were administered 20 mg of HB as a subcutaneous bolus or intravenously, followed by 60 mg/24 hours (subcutaneous 20 mg every eight hours or continuous intravenous/subcutaneous infusion). Opioids were maintained, if previously given for other reasons (pain or dyspnea), via nonoral routes. Symptomatic agents, commonly used in the last days of life (e.g.,

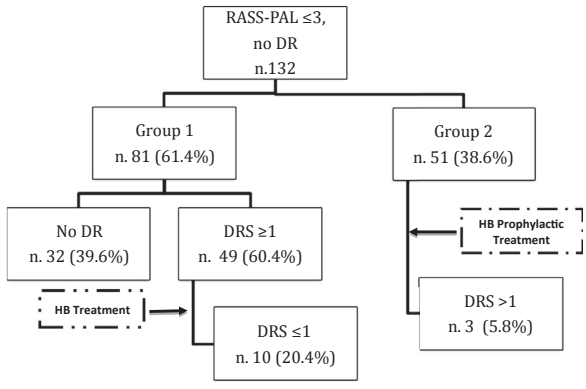

Fig. 1. Patients' flowchart, according to study design. RASS-PAL = Richmond Agitation-Sedation Scale—palliative version; DR = death rattle; DRS = death rattle score; HB = hyoscine butylbromide.

diuretics and neuroleptics, other sedative drugs), were administered when necessary. Drugs and doses were changed according to the clinical need, with no strict protocol. Intravenous hydration was reduced to 10 mL/hour of saline.

The rattle intensity score was considered as follows: 0 = not audible, 1 = only audible near the patient, 2 = clearly audible at the end of the patient's bed in a quiet room, and 3 = clearly audible at a distance of about 9.5 m (at the door of the room) in a quiet room.[13]

After the treatment began, all patients were clinically evaluated by the nurse in charge at predefined time points: 30 minutes, one hour, and then every six hours until death. The onset of DR (death rattle free time [DRFT]) was recorded. The treatment was considered effective when the intensity of the rattle was 0 or 1 or with an improvement of at least one point in the score. With a rattle intensity of 2 or 3, or no change in intensity, the treatment was considered ineffective.

Statistical Methods

For sample size, for each arm of the research, a small Cohen effect size was used.[14] The sample size estimation was affected by an expected dropout in Group 1, because of the drug administration inclusion criteria, of 65%, so that we had to adjust for this unbalancing in our study arms.[15] Group probability assignment was given a priori from sample size estimated. The block randomization code was masked to the clinician.

The primary efficacy analysis will be the end point that was analyzed by covariance (analysis of covariance) model; the treatment comparisons between the two groups have been tested at a two-sided 0.005 level of significance. Descriptive statistics by treatment groups was provided for all efficacy end points. Descriptive statistics on continuous measurements included means, medians, SDs, and ranges, whereas categorical data were summarized using frequency counts and percentages.

The analysis addressed the issue of assessing a difference between the control and treated groups. Descriptive explorative analysis was provided for the sample statistics during the trial follow-up. At the onset, arms homogeneity of the covariates was assessed using a Hotelling T^2 multivariate test. Homogeneity in case of nominal variables was assessed using χ^2 tests. DR pattern difference according to the trial arms was tackled using a survival analysis. DRFT, that is time up to the first occurrence of DR, was used to build up Kaplan-Meier survival curves corresponding to the trial groups. Median DRFT and interquartile ranges for each group were provided ($\alpha = 0.05$). Kaplan-Meier curves were compared using the log rank test. The analysis was carried out using the STATA (version 14) statistical software (StataCorp, College Station, TX).

Results

One hundred thirty-two patients with an RASS-PAL score of ≤3 were randomized to receive the study drug. Eighty-one patients received HB after the occurrence of DR (Group 1), and 51 patients received prophylactically HB (Group 2), according to the randomization process (Fig. 1).

The general characteristics of patients are listed in Table 1. Patients in Group 2 survived longer than those in Group 1 ($P < 0.05$). No other statistical differences were found. In particular, the RASS-PAL and the number of patients who were receiving palliative sedation did not differ between the two groups. The drugs used at time of randomization are reported in Table 2. Antiepileptics had been more prescribed in Group 2. No other significant differences were found between the two groups.

From the time of randomization to death, DR occurred in 49 patients (60.5%) and three patients (5.9%) in Group 1 and 2, respectively ($P = 0.001$). The number of patients and the intensity of DR, as well as RASS-PAL, are reported in Table 3. A significant difference in the number of patients reporting DR was found at the intervals examined ($P = 0.001$). No differences in RASS-PAL and DR intensity were found. In Group 1, the mean DRFT was 20.4 hours (SD 20.53), and median was 12 (6−30). In Group 2, the mean DRFT was 27.3 hours (SD 25.2), and the median was 36 (12−66). The difference was significant ($P = 0.0001$) (Fig. 2). In Group 1, the treatment was considered effective in 10 patients (20.4%) only. The response was considered positive after a mean of 14.4 hours (SD 8.57) and median of 12 (6−24).

Discussion

This study showed that HB, given prophylactically in the dying patient with a spontaneous decrease in the level of consciousness or induced by palliative sedation, is an effective strategy in preventing DR. HB given after the development of DR was frequently ineffective. Thus, although the design was not exactly a randomized controlled trial, as HB was given to both groups, it suggests that the modality of an anticipatory treatment is highly effective in comparison with HB given even as soon as DR develops. After that, the number of patients with DR did not decrease, with no significant changes in DR score until death. The treatment was considered effective only in about 20% of patients. Indeed, the pre-emptive

Table 1
Characteristics of Patients

Characteristic	Overall	Group 1	Group 2	*P*
Age (yrs); mean (SD)	74.5 (12.73)	73.8 (12.46)	75.6 (13.23)	0.41
Gender (F/M)	55/77	33/48	22/29	0.61
Primary tumor, *n* (%)				
Lung	20 (15.1)	13 (16.0)	7 (13.7)	0.39
Breast	9 (6.8)	5 (6.2)	4 (7.8)	
Gastrointestinal	57 (43.2)	39 (48.1)	18 (35.3)	
Pancreas	21 (15.9)	12 (14.8)	9 (17.6)	
Urological	13 (9.8)	6 (7.4)	7 (13.7)	
CNS	7 (5.3)	2 (2.5)	5 (9.8)	
Other	5 (3.8)	4 (4.9)	1 (2.0)	
Palliative sedation, *n* (%)	90 (68.2)	54 (61.4)	36 (40.0)	0.64
Diuresis (mean)	1219.5 mL (958.6)	1171.4 mL (113.2)	1303.7 mL (155.7)	0.49
RASS-PAL (median)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −5)	
Survival (mean)	41.28 hours (27.44)	41.10 hours (26.61)	45.26 hours (28.81)	0.05

F = female; M = male; CNS = central nervous system; RASS-PAL = Richmond Agitation-Sedation Scale—palliative version.

administration of HB prevented the occurrence of DR in almost all patients, given that about 10% only developed DR. Of interest in Group 1, about 50% of the patients developed DR.

It has been reported that patients at particular risk of DR are those with prolonged dying phase,[1,4] and patients with high rattle scores have a shorter survival.[2] Postulated mechanism for DR is because of the loss of reflexes for coughing and swallowing, hence pooling of secretions. The loss of these reflexes is the consequence of a spontaneous neurological derangement or simply because palliative sedation is started.[6]

In the existent literature, patients have been treated with formed secretions that cannot longer be managed with anticholinergic drugs, able only to reduce the formation of new secretions, but not having an effect on existing secretions. This clinical and pharmacological observation can explain the controversial results, including the lack of effects or the poor differences between anticholinergic drugs and placebo. In recent reviews assessing the role of anticholinergics for treating DR, no evidence was found that anticholinergics were superior to placebo.[10,16] Data reported in the arm of the traditional use of HB of the present study are consistent with these data. Regardless of the limitations of these studies, justified by the difficult clinical situation, different assessment tools, variable doses of anticholinergics, low number of patients, limited time to measure the efficacy of a treatment, as well as missing observations, data were difficult to judge. In all the cases, drugs have been used to treat noisy secretion rather than preventing the formation. The anticipated administration of HB in the context of imminent death, before starting palliative sedation, or in the presence of incapacity to swallow or cough, may be a meaningful perspective.[11]

This study has some limitations. One could argue that some patients would have never developed DR, even without pre-emptive HB. In Group 1, in which patients have been traditionally treated, DR developed in 35% of patients after 18 hours and in 51% of patients after 36 hours. At the same intervals, when HB was given prophylactically, no patient and 10%, respectively, developed DR. The sample size and protocol used aimed to compensate the numbers, also considering the expected dropout in patients who were administered HB when DR developed, because of the drug administration inclusion criteria. Potentially,

Table 2
Drugs Given at T0

	Overall	Group 1	Group 2	*P*
Opioids, *n* (%)				
None	8 (6.1)	7 (8.6)	1 (2.0)	
Morphine	99 (75.0)	56 (69.1)	43 (84.3)	0.08
Fentanyl	24 (18.2)	18 (22.2)	6 (11.7)	
Methadone	1 (0.8)	0	1 (2.0)	
Dose of opioids (oral morphine equivalents) mg/day	129.6 (161.5)	145.0 (194.8)	106.9 (89.7)	0.20
Diuretics, *n* (%)	80 (60.6)	49 (60.5)	31 (60.8)	0.97
Antiepileptics, *n* (%)	14 (10.6)	4 (4.9)	10 (19.61)	0.01
Corticosteroids, *n* (%)	76 (57.6)	45 (55.6)	31 (60.8)	0.55
Metoclopramide, *n* (%)	30 (22.7)	22 (27.2)	8 (15.7)	0.13
Benzodiazepines, *n* (%)	91 (68.9)	51 (62.9)	40 (78.4)	0.06

Table 3
Number of Patients With DR, Intensity of Death Rattle (DRS), and RASS-PAL at the Various Intervals Examined

	T0	30'	One Hour	Six Hours	12 Hours	18 Hours	24 Hours	36 Hours	48 Hours	60 Hours	66 Hours
Overall											
No. of patients	132	132	129	126	107	92	85	73	61	45	45
DR, *n* (%)	0	4 (3.0)	7 (5.4)	24 (19.0)	24 (22.4)	20 (21.7)	21 (24.7)	26 (35.6)	16 (26.2)	13 (28.9)	12 (26.7)
DRS (mean)	0	1 (0)	1.28 (0.49)	1.37 (0.49)	1.25 (0.44)	1.20 (0.52)	1.19 (0.51)	1.04 (0.20)	1.25 (0.58)	1.31 (0.75)	1 (0)
RASS-PAL	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −5)	−4 (≤3, −5)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (−4, −5)	−4 (−4, −5)
Group 1											
No. of patients	81	81	78	76	65	56	52	45	37	25	25
DR, *n* (%)	0	4 (4.9)	7 (9.0)	24 (31.6)	24 (36.9)	20 (35.7)	21 (40.4)	23 (51.1)	15 (40.5)	13 (52.0)	12 (48.0)
DRS (mean)	0	1 (0)	1.29 (0.49)	1.35 (0.49)	1.25 (0.44)	1.2 (0.52)	1.19 (0.51)	1.04 (0.21)	1.2 (0.56)	1.3 (0.75)	1 (0)
RASS-PAL	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (≤3, −4)	−4 (−4, −4)	−4 (−4, −4)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)
Group 2											
No. of patients	51	51	51	50	42	42	33	28	24	20	20
DR, *n* (%)	0	0	0	0	0	0	0	3 (10.7)	1 (4.2)	0	0
DRS (mean)	0	0	0	0	0	0	0	1	1	0	0
RASS-PAL	−4 (≤3, −5)	−4 (≤3, −5)	−4 (≤3, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −5)	−4 (−4, −4)	−4 (−4, −4)

DR = death rattle; DRS = death rattle score; RASS-PAL = Richmond Agitation-Sedation Scale—palliative version.

Fig. 2. Death rattle free time. Kaplan-Meier curves of the two groups. The difference was significant ($P = 0.0001$).

the trial could include a placebo arm, but this kind of study is difficult to afford in extreme situations, as in the dying patient. Thus, it was considered acceptable that a comparison with a standard use of HB used to control DR, which means a comparison regarding the modality and timing of HB administration.

In conclusion, the pre-emptive use of HB is an efficient method to prevent the formation of pharyngeal-tracheal secretions, whereas the late administration, once the secretions are already present, does not produce an effective response, confirming data from traditional studies performed with anticholinergics. This could be considered a new paradigm to manage a difficult and dramatic sign, such as DR. Further studies with an appropriate design should be performed to confirm the results of the present study. A placebo-controlled trial according to the pre-emptive protocol may be helpful, although the use of placebo in an extreme condition such as that of a dying patient is really difficult to perform.

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