Continuous deep sedation: Physicians' experiences in six European countries

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ABSTRACT

Background

Continuous deep sedation (CDS) is sometimes used to treat refractory symptoms in terminally ill patients. The aim of this paper was to estimate the frequency and characteristics of CDS in six European countries: Belgium, Denmark, Italy, the Netherlands, Sweden and Switzerland.

Methods

Deaths reported to death registries were sampled and the reporting doctors received a mailed questionnaire about the medical decision-making that preceded the death of the patient.

Findings

The total number of deaths studied was 20,480. The response rate ranged between 44 percent (Italy) and 75 percent (the Netherlands). Of all deaths, CDS was applied in 2.5 percent in Denmark and up to 8.5 percent in Italy. Of all patients receiving CDS, 35% (Italy) and up to 64% (Denmark and the Netherlands) did not receive artificial nutrition or hydration. Patients who received CDS were more often male, younger than 80 years old, more likely to have had cancer, and died more often in a hospital compared to non-sudden deaths without CDS.

Interpretation

The high variability of frequency and characteristics of continuous deep sedation in the studied European countries points out the importance of medical education and scientific debate on this issue.

[Words 193]

Continuous deep sedation in Europe

Key words: sedation, palliative care, medical end-of-life decisions

Introduction

Severe symptoms, sometimes defined as ‘refractory’, have high prevalence during the last days of life among terminal oncology and other diseases (1, 2, 3). In such cases, sedation is an accepted procedure in palliative care (4). In general, deep sedation is to be used only temporarily (5); nonetheless, continuous deep sedation (CDS) may be the only means to control symptoms (6).

It is already known that sedatives are rather frequently used to treat severely suffering patients nearing death. Within palliative care settings incidence estimates of the use of sedatives range from 15% to more than 60% (7-13). Furthermore, a survey among palliative care specialists in North America and the U.K. showed that 77% of the respondents had at one time applied deep sedation in patients close to death (14) and a study from Japan showed that 64%-70% of a sample of palliative care physicians and oncologists reported having used some form of deep sedation for severe physical distress (15). However, these estimates are difficult to compare due to differences in the settings studied and the definitions used. CDS without administering artificial nutrition/hydration is, by some authors, considered as a special kind of sedation (‘terminal sedation’) due to the intended or foreseen life-shortening effect (16,17).

To gain more insight into the practice of CDS, more information on characteristics of sedated patients would be helpful. Previous studies reported that important indications for the use of sedatives in patients nearing death are intractable pain, dyspnea, delirium, agitation, and severe psychological symptoms such as anxiety and existential distress (7,10-12,14,18,19). A nationwide Dutch study found that half of the cases of terminal sedation were performed by clinical specialists; 30% of the patients receiving terminal sedation were 80 years of age or older, and 54% were concerned patients with cancer (18). However, further detailed and reliable information about characteristics of patients who receive CDS is needed because most studies were performed in a specific setting or focussed on specific groups of patients.

In a recent death-certificate study about end-of-life decision-making in six European countries (EURELD) (20), physicians were also asked about the use of CDS. In this paper, we aim to presenting comparable population-based estimates for Belgium (Flanders), Denmark, Italy (four areas), the Netherlands, Sweden and Switzerland (German-speaking part) regarding the use of CDS -with and without the administration of artificial nutrition and hydration- and to describe the characteristics of patients receiving CDS.

Methods

Design

In every participating country or region random samples of death certificates of people aged 1 year or older (Italy: 18 or older) were obtained from death registries. The sampling period varied from 3 to 6 months. All deaths arose between June 2001 and February 2002. In all countries (apart from Switzerland) all deaths reported during the sampling period were stratified for the likelihood that death had been preceded by an end-of-life decision. Based on the cause of death, all deaths were assigned to one of three (Belgium, Denmark, Italy and Sweden) or five (the Netherlands) strata. Sampling fractions were higher for strata in which the cause of death made an end-of-life decision more likely. Stratification was applied to enhance the efficiency and to yield smaller confidence intervals around estimates. Details have been described elsewhere (20). In all countries the data-collection procedure precluded identification of any of the doctors or patients. A clearinghouse, usually a notary's office, was interposed in each participating country. No envelope that contained a returned questionnaire reached the researchers before all identifying information had been removed from the data set using a separate code system. An application to the Research Ethics Committee (REC) was required in all countries except in Denmark (where questionnaire research only has to be assessed by a REC if it is part of a project involving biomedical research), in Switzerland (cantonal authority for data security confirmed anonymity of the data used in the study), and in the Netherlands (where the Royal Dutch Medical Association and the Health Inspectorate approved of the study) (21).

Questionnaire

For all sampled cases the attending physicians were asked if death had occurred suddenly and unexpectedly. If cases were reported to have been non-sudden, the attending doctors were asked to fill out a four-page written questionnaire about the medical decision-making that had preceded the death involved. The penultimate item in the questionnaire dealt with CDS: "Did the patient receive drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death?" Answering options were: "yes, and artificial nutrition and hydration were not given"; "yes, and artificial nutrition or hydration were given"; "no". This question was asked for all non-sudden deaths, except in the Netherlands, where, due to a routing difference, the question was asked only if an end-of-life decision preceded death.

Statistical analyses

If applicable, results were corrected for stratification by giving all cases a weight that is the reverse of the sampling fraction within the stratum they were assigned to. To allow the results to be representative of all deaths in the studied period an additional weight was calculated from age, sex, cause of death and place of death specific response rates. Absolute frequencies and weighted percentages on total studied deaths were reported. The prevalence of CDS was compared for different classes of sex, age, cause of death, and place of death. To calculate estimates for all countries together, an additional country-specific weighting factor (the inverse of the weighted number of deaths studied in each country) was applied. The statistical significance of differences in CDS prevalence was estimated by means of Pearson chi-squared statistic corrected for the survey design (22). A logistic regression was fitted to the data to determine the independent association of each characteristic of deaths with CDS. The model considered non-sudden deaths without CDS as controls. Likelihood ratio tests were used to test statistical interactions. All the statistical analyses were made using the ‘svy commands’ of the statistical package STATA , release 8 (23).

Results

20,480 deaths could be studied for which a questionnaire was sufficiently filled out and returned.

Response percentage ranged from 59% to 75%, except for Italy (44%).

Table 1 shows that Italy and Belgium reported the highest percentages of CDS: 8.5% and 8.2% of all deaths, respectively, were preceded by the use of CDS. Denmark and Sweden reported the lowest frequencies: 2.5% and 3.2%, respectively, and Switzerland was somewhat in between (4.8% of all deaths). The prevalence of CDS while artificial nutrition and hydration were withdrawn or withheld varied less between countries (range 1.6% - 3.2%, Denmark and Belgium respectively). Of all sedated patients, 35%-64% did not receive artificial nutrition or hydration (Italy and Denmark/The Netherlands, respectively).

Table 2 shows characteristics of deaths in which CDS was applied. Cancer was the cause of death with the highest prevalence of CDS in all countries. In all countries, CDS was less frequently applied in patients older than 80 years old and more frequently in hospitals.

In a multivariate analysis that considered all countries together, each characteristic of the patients was independently associated to CDS (see table 3). The probability of receiving CDS was increased in males by 17%, in patients dying from cancer by 15%, in patients 65-79 years old by 91%, in patients younger than 65 years old by 134%, and in patients dying in the hospital by 63%. Statistically significant ($P < 0.01$) interactions were found between age and cause of death (effects of age and hospital were reduced in patients dying of cancer).

Discussion

Our study has, for the first time, enabled an international estimation to be carried out on the incidence of the use of drugs to keep patients in continuous deep sedation (CDS) in a large sample of non-selected patients from six European countries. CDS is practiced in all countries, in hospitals as well as in other settings of care, for cancer patients as well as for other kinds of patients.

The finding that CDS is a frequently applied practice is in line with other studies conducted in palliative care settings (1, 7-13). It was expected that the estimates at a population level would have been lower than those observed in specialist palliative care settings. Another reason why our estimates are not fully comparable with other studies is that the definition of CDS we used excluded secondary and mild sedation, or intermittent deep sedation. The Dutch figures in our study are somewhat lower than those observed in another Dutch study at a population level, which reported that 10% of all deaths were preceded by terminal sedation (18). This can probably be explained by the fact that in our study the Dutch data only included cases in which an end-of-life decision was made.

Inter-country variations in total frequency were mainly due to variations in the use of CDS with continuing the administration of artificial nutrition or hydration. It can be expected that in such cases the main intention is to relieve intolerable suffering and not to hasten death. Italy and Belgium have the highest estimates of CDS with artificial nutrition or hydration. It is possible that this result depends on the Catholic tradition of those countries, in which there is a widespread acceptance of the sanctity of life doctrine. Another explanation for the differences in frequency of CDS with artificial nutrition and hydration between the countries could be that there is variation in the moment when CDS is started. High frequency of CDS with artificial nutrition and hydration could be an indication that the patient is not in the dying phase yet. However, this hypothesis needs more research since we cannot conclude this from our data.

Since the first report on CDS in palliative care the appropriateness of using sedating drugs to control ‘refractory’ symptoms in imminently dying patients has been brought to light (1,4). At the same time an ethical debate has been emerging about the possible life-shortening effects of this medical procedure (9, 10, 14, 17, 24-25). We found that in 35% - 64% of all CDS cases, the patient did not receive artificial nutrition and hydration. The Netherlands, where the question on CDS was asked only if an end-of-life decision preceded death, had the highest proportion of CDS without artificial nutrition and hydration, together with

Denmark. We also know from a recent study that in the Netherlands 17% of CDS without artificial nutrition and hydration were performed with the explicit intention of hastening death, mainly by means of forgoing artificial nutrition and hydration (18). In medical and ethical discussions it is debated whether forgoing artificial nutrition and hydration in deeply sedated patients shortens life, and if so, whether this should be considered as acceptable medical practice. The issue is controversial, also because forgoing artificial nutrition and hydration can sometimes be clinically indicated in imminently dying patients (5), and because sedation in terminally ill cancer patients has not been proved to be substantially influential on the duration of residual survival (26). However, when the patients' estimated life expectancy is more than a week, forgoing artificial nutrition or hydration in deeply sedated patients has been indicated as a possible marker of an intention to hasten death (16, 27).

CDS is clinically indicated for imminently dying patients with severe symptoms refractory to conventional palliative treatments. It is not surprising that it was more often performed in cancer patients and in hospital settings, where there are more dying patients with the worst clinical conditions. The Italian exception (CDS more often in non-hospital settings) may be motivated by the rather high diffusion of domiciliary palliative care in the areas participating to the EURELD study. It's more difficult to find an explanation for the higher frequency of male patients among sedated patients. As far as the younger age of sedated patients is concerned this result confirms other observations reported in the literature (18) and was more prevalent in our data among non cancer patients.

Our study has some limitations. We cannot exclude the possibility that non-response has to some extent biased our result, especially for Italy. Further, our results probably cannot be extrapolated to other than the regions studied in Belgium, Switzerland and Italy. Although our definition of CDS was quite strict, excluding the secondary, intermittent and mild sedation, we did not ask for the specific intention of the reported sedation, for the specific drugs used or for the presence of refractory symptoms.

To conclude, the substantial practice of CDS in and outside hospitals, and the cross-national differences point out the importance of further scientific debate and medical education on these medical procedures. Developing and implementing practice guidelines could contribute to assure high quality of this practice, and its appropriate use (i.e. after having considered all the other options and mainly the present palliative

treatments available). Further studies will be necessary to describe the costs and benefits of CDS in terms of quality of dying.

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Table 1 Frequency of continuous deep sedation (CDS) in six European countries, by presence of artificial nutrition and hydration (ANH).

	Belgium		Denmark		Italy		The Netherlands[§]		Sweden		Switzerland	
Response percentage	59		62		44		75		61		67	
Studied deaths	2,950		2,939		2,604		5,384		3,248		3,355	
CDS with ANH	120	5.0 (4.2-6.1)	24	0.9 (0.5-1.3)	191	5.5 (4.7-6.5)	89	2.0 (1.6-2.6)	52	1.4 (1.0-1.8)	64	1.9 (1.5-2.4)
CDS without ANH[‡] (A)	118	3.2 (2.6-3.0)	62	1.6 (1.3-2.2)	123	3.0 (2.4-3.6)	247	3.7 (3.2-4.2)	74	1.8 (1.4-2.3)	96	2.9 (2.3-3.5)
Total CDS (B)	238	8.2 (7.1-9.4)	86	2.5 (2.0-3.2)	314	8.5 (7.5-9.6)	336	5.7 (5.0-6.4)	126	3.2 (2.6-3.9)	160	4.8 (4.1-5.5)
Ratio A/B	0.39		0.64		0.35		0.64		0.56		0.60	

Frequencies of CDS, weighted percentages of CDS on total studied deaths and (95% confidence intervals).
§ Due to a routing difference, Dutch data refer only to deep sedation until death which occurred together with another end-of-life decision.
‡ CDS without ANH includes both withdrawing and withholding artificial nutrition and hydration.

Table 2 Characteristics of deaths in cases of continuous deep sedation (CDS) in six European countries.

	Belgium		Denmark		Italy		The Netherlands[§]		Sweden		Switzerland		All countries	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex														
Male	133	9.2	48	3.1	170	9.4	159	5.8	62	3.6	80	4.8	652	6.0
Female	105	7.1	36	1.9	141	7.6	177	5.5	61	2.7	80	4.7	600	4.9
P value[#]		*0.059*		*0.046*		*0.103*		*0.665*		*0.121*		*0.866*		*0.001*
Age (years)														
<65	67	11.4	26	4.4	72	14.0	98	6.7	31	6.2	32	5.4	326	3.8
65-79	113	11.6	35	2.4	133	10.1	137	7.6	56	4.5	53	5.4	527	7.0
80+	58	4.7	23	1.8	107	6.3	101	3.7	36	1.7	75	4.2	400	7.7
P value[#]		*<0.001*		*0.006*		*<0.001*		*<0.001*		*<0.001*		*0.271*		*<0.001*
Cause of death[¤]														
Cardiovascular dis.	36	7.5	12	2.2	29	4.6	28	2.9	26	2.0	30	2.5	161	3.5
Malignant dis.	127	9.9	55	4.0	260	16.3	155	6.6	79	5.0	74	9.0	750	8.7
Respiratory dis.	25	8.8	6	2.9	3	2.9	26	6.1	3	2.5	10	3.5	73	4.7
Nervous System dis.	16	7.2	6	2.6	8	14.8	25	4.4	1	2.9	23	6.4	79	5.6
Other/unknown	34	7.4	7	0.9	13	4.5	102	7.5	15	3.5	23	3.4	194	4.6
P value[#]		*0.4781*		*0.019*		*<0.001*		*<0.001*		*0.002*		*<0.001*		*<0.001*
Place of death														
Hospital	160	13.2	36	2.9	138	8.3	107	7.7	83	5.0	92	7.4	616	7.7
Other[‡]	78	3.2	50	2.2	175	8.8	229	4.7	39	1.6	68	3.2	639	3.9
P value[#]		*<0.001*		*0.267*		*0.652*		*<0.001*		*<0.001*		*<0.001*		*<0.001*

Frequencies of CDS and weighted percentages of CDS on total studied deaths

§ Due to a routing difference, Dutch data refer only to deep sedation until death which occurred together with another end-of-life decision.

P value of Pearson chi-squared statistic (corrected for the survey design). Significance of difference in CDS prevalence, amongst the categories of the characteristics (sex, age, cause of death, place of death) of deaths.

¤Cerebrovascular disease is included in cardiovascular diseases for Italy and Sweden and in diseases of the nervous system for Belgium, Denmark, the Netherlands, and Switzerland.

‡ 'Other' place of death includes both home and institution

Table 3 Determinants of continuous deep sedation (CDS) in six European countries. Logistic regression, non-sudden deaths only, all countries together.

	RR	95% C.I.
Sex		
Male	1.17	1.02-1.34
Female	1	
Age (years)		
<65	2.34	1.93-2.85
65-79	1.91	1.62-2.25
80+	1	
Cause of death		
Malignant diseases	1.15	1.00-1.33
Other diseases	1	
Place of death		
Hospital	1.63	1.43-1.86
Other‡	1	

‡ 'Other' place of death includes both home and institution