Deep continuous patient-requested sedation until death: a multicentric study

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ABSTRACT

Objectives In 2016, a new law was adopted in France granting patients the right, under specific conditions, to continuous deep sedation until death (CDSUD). The goal of this study was to measure the frequency of requests for CDSUD from patients in palliative care.

Methods The data collected from the medical records of patients in palliative care units (PCU) or followed by palliative care support teams (PCST) in the Rhône-Alpes area, who died after CDSUD, focused on the patient's characteristics, the drugs used (and compliance with regulatory processes).

Results All 12 PCU and 12 of the 24 PCST were included. Among the 8500 patients followed, 42 (0.5%) requested CDSUD until death. The patients were: 65.7 (SD=13.7) years old, highly educated (69%), had cancer (81%), refractory symptoms (98%) and mostly psychoexistential distress (69%). The request was rejected for 2 (5%) patients and delayed for 31 (74%) patients. After a delay of a mean 8 days, 13 (31%) patients were granted CDSUD. The drug used was midazolam at 115 mg/24 hours (15–480), during a mean of 3 days. PCUs used lower dosages than PCSTs (83 vs 147), with significantly lower initial doses (39 mg vs 132 mg, p=0.01). A life-threatening condition was recorded in 13 cases (31%) and a collegial decision was taken in 25 cases (60%).

Conclusion This study highlights the low rate of request and the even lower rate of CDSUD in specialised palliative care. However, the sedation for psychoexistential distress and the lack of procedure records raise ethical questions.

INTRODUCTION

Since 2016, a new French law has given the patient the right, on his/her request, to obtain continuous deep sedation until death (CDSUD) under certain conditions, namely: severe and incurable disease, short-term prognosis, refractory symptoms, or the decision to discontinue treatment that may result in unbearable suffering,[1 2] and raise controversies even outside the country.[3] This new law has led to new requests from patients, and questions the sedation practices of all services, including palliative care. Palliative sedation is used in palliative care and numerous recommendations have been published.[4] Palliative sedation is defined as 'The intentional administration of sedative drugs in dosages and combinations required to reduce the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms.'[5] Palliative sedation is prescribed in palliative care to relieve unbearable refractory symptoms, and the level of the sedation is transitory, proportionate and sometimes reversible under certain conditions.[6 7] The CDSUD requested by the patient is a different practice even if the word sedation is the same: the sedation is deep, that is, 4 or 5 of the Richmond Agitation-Sedation Scale, regardless of the level of distress and will continue until death, that is, it is not reversible, which raises ethical questions.[3 8] The difference between CDSUD and euthanasia is based on the dosage of the sedative drug and thus on the intentionality of the prescriber.[9] The prevalence of continuous deep sedation seems to vary according to complex legal, cultural and organisational factors more than according to differences in patients' characteristics or clinical profiles.[10] For some, CDSUD is already considered a 'social euthanasia'.[11]

The goal of this study is to assess the frequency of the request for CDSUD in the palliative care units (PCU) and

palliative care support teams (PCST) of the Rhône-Alpes area, the context of the request, as well as the responses of the palliative teams.

METHODS

This study is a retrospective, observational multicentric survey. Medical records of all patients who died in palliative care services in the Rhône-Alpes area who asked for CDSUD until death from August 2016 to August 2017 were reviewed by the researcher (AS) in collaboration with the physician in charge. The demographic data were recorded as usual, and the data related to the psychological patient profile and the request context were collected in collaboration with the physician in charge and team member if needed. The data collected focused on patient characteristics (age, gender, educational level, financial difficulties, control profile—defined as the way the patient needs to have control over his life—, spirituality—defined as the patient's attachment to religious or other spiritual support—, performance status (PS), pathology, systematic screening for depression, or depression symptoms registrated in the patient chart, refractory symptoms) and the context of demand (initial demand for euthanasia, intensity of the request, ambivalence, triggers— defined as events probably linked to the CDSUD request, such as the announcement of the disease progressing, eg, invasive equipment, pressure from the family). The responses of the palliative teams (rejection, delay without CDSUD, delay followed by CDSUD or immediate CDSUD) were collected. Immediate CDSUD was considered when the delay between the request and CDSUD was less than 72 hours. The palliative intervention was recorded. When CDSUD was performed, data on the drugs used, average dosage, initial and final, and duration of the administration were collected. The ethical and regulatory aspect was sought (short-term prognosis, collegial decision record, advance directives, trusted person).

Statistical analysis

Before analysis, the database was anonymised. Statistical analyses were conducted using Epi Info V.7.1.5.2 and Microsoft Excel V.2010. Descriptive statistics were used to estimate the frequencies, means (SD) in case of normally distributed variables and as median (IQR or minimum–maximum range) in case of non-normally distributed variables. Differences between the groups were assessed with the use of two-sided Fisher's exact tests and χ^2 tests for categorical variables and independent-samples Student's t-tests for continuous variables. A p value of\ 0.05 (two sided) was deemed statistically significant.

The protocol of the study was accepted by the Institutional Review Board of our institution on 2 July 2017.

RESULTS

All 12 PCUs and 12 of the 24 PCSTs from the Rhône-Alpes region were included in the study from 15 August 2016 to 14 August 2017. Among the 8500 patients followed by palliative care services, 42 (0.5%) made a request for CDSUD until death, 23 (55%) in PCUs and 19 (45%) in PCSTs. Sixty-four per cent of these requests were made following a request for euthanasia.

The characteristics of patients requesting CDSUD are described in table 1.

They comprised 21 (50%) male, 65.7 years old (SD=13.7), 29 (69%) with a level of study higher than pregraduate, 31 (74%). Patients had a 'control profile', serious and incurable disease (100%) including cancer for 34 (81%) patients, mainly gastrointestinal 13 (31%), gynaecological 7 (17%) and lung cancer 7 (17%), and amyotrophic lateral sclerosis (ALS) 6 (14%) or organ failure 2 (4%). Of patients with refractory symptoms, 41 (98%) recorded, we found psychoexistential distress in 29 (69%), pain 18 (43%), dyspnoea 17 (41%), major anxiety 14 (33%) and nausea-vomiting-occlusion 10 (24%). In half of the requests for CDSUD, the notion of 'loss of control', *being* defined by the patient sentences or during the physician in charge's interview, was recorded. The PS was 3 or 4 for 31 (74%) patients. In addition, nine (21%) of the patients had invasive equipment (tracheotomy, nephrostomy, gastrostomy, ventilation, nasogastric tube). A major depressive state was present in 38%, untreated in 17%. Depression was not assessed in 33% of patients. A triggering element was found in 25 (60%) of cases: acute distressing symptom as a flare of pain, severe dyspnoea crisis, the announcement of bad news as the cancer had progressed, therapeutic failure or worsening prognosis. Ambivalence was present in 20 (48%) of patients' requests. In all these cases CDSUD was delayed. Data about patient spirituality were never recorded, even in the case of psychoexistential suffering.

The responses of palliative teams are described in table 2.

The request for CDSUD was rejected for two patients (5%). CDSUD was carried out after less than 72 hours in nine (21%) patients without significant difference between PCUs and PCSTs. No CDSUD was performed in 18 (43%) of cases and CDSUD was performed for 13 (31%) patients after a delay of 12 days on average. Hydration or other life supporting therapies were always withdrawn as requested in the French law. The time delay was longer in PCUs than in PCST s (11 vs 5 days, p=0.06).

In the case of delays, an adaptation of the drug treatments was found in 37 (88%) patients. Increasing opioids or opioid rotation was found in 30 (71%) patients, antidepressants were prescribed in 9 (21%) of cases, midazolam for anxiety in 26 (62%) patients and 3 (7%) patients had intermittent sedation. Reinforcement of palliative care with psychological care, psychological support by volunteers, and psychocorporeal approaches was proposed in 29 (69%) of cases (psychological support 69%, volunteers 45%, massage

Table 1 Patient characteristics and background of CDSUD requests

	Rejection (n=2)	Delay then no CDSUD (n=18)	Delay then CDSUD (n=13)	Immediate CDSUD (n=9)	Total (n=42)
Sex, male	0	9 (50)	7 (54)	5 (56)	21 (50)
Age in years, mean	56 (SD=6)	68.7 (SD=13)	66.1 (SD=10.1)	61.4 (SD=20	65.7 (SD=13.7)
College education level+	1 (50)	13 (72)	10 (77)	5 (56)	29 (69)
Financial difficulties	1 (50)	0	1 (8)	0	2 (5)
Control profile	2 (100)	13 (72)	10 (77)	6 (67)	31 (74)
Spirituality	0	0	2 (15)	0	2 (5)
Social isolation	0	1 (6)	1 (8)	0	2 (5)
Performance status					
1	0	2 (11)	2 (15)	0	4 (9)
2	0	1 (6)	4 (31)	2 (22)	7 (17)
3	1 (50)	9 (50)	4 (31)	4 (44)	18 (43)
4	1 (50)	6 (33)	3 (23)	3 (33)	13 (31)
Pathology					
Cancer	1 (50)	16 (89)	9 (69)	8 (89)	34 (81)
Digestive	0	10 (56)	2 (15)	1 (11)	13 (31)
Gynaecological	1 (50)	2 (11)	3 (23)	1 (11)	7 (17)
Pulmonary	0	0	1 (8)	3 (33)	4 (10)
Head and neck	0	0	2 (15)	0	2 (5)
Brain	0	2 (11)	0	0	2 (5)
Haematological	0	0	0	2 (22)	2 (5)
Urological	0	0	0	1 (11)	1 (2)
Sarcoma	0	0	1 (8)	0	1 (2)
Primary unknown	0	1 (6)	0	0	1 (2)
Skin	0	1 (6)	0	0	1 (2)
ALS	1 (50)	2 (11)	3 (23)	0	6 (14)
Cystic fibrosis	0	0	0	1 (11)	1 (2)
Respiratory failure	0	0	1 (8)	0	1 (2)
Symptoms*	2 (100)	17 (94)	13 (100)	9 (100)	41 (98)
Psychoexistential suffering	2 (100)	12 (67)	12 (92)	5 (56)	29 (69)
Pain	1 (50)	9 (50)	6 (47)	3 (33)	18 (43)
Dyspnoea	0	6 (33)	5 (38)	5 (56)	17 (41)
Major depressive state	2 (100)	6 (33)	5 (38)	3 (33)	16 (38)
Major depressive state untreated	1 (50)	2 (11)	2 (15)	2 (22)	7 (17)
Depressive state non-assessed	0	7 (39)	3 (23)	4 (44)	14 (33)
Major anxiety	0	8 (44)	4 (31)	2 (22)	14 (33)
Nausea-vomiting/diarrhoea/ occlusion	0	5 (28)	1 (8)	3 (33)	10 (24)
Agitation	0	0	1 (8)	0	1 (2)
None	0	1 (6)	0	0	1 (2)
Context of the request					
Initial request for euthanasia	1 (50)	11 (61)	9 (69)	6 (67)	27 (64)
Ambivalence	2 (100)	11 (61)	7 (54)	0	20 (48)
High-intensity demand	0	13 (72)	11 (85)	9 (100)	33 (79)
Ambivalence and high-intensity demand	0	9 (50)	5 (38)	0	14 (33)
Trigger	1 (50)	8 (44)	9 (69)	7 (78)	25 (60)
Invasive equipment	0	3 (17)	3 (23)	4 (44)	9 (21)
Pressure of the entourage	1 (50)	2 (11)	5 (38)	3 (33)	11 (26)
Cognitive disorders	0	1 (6)	1 (8)	0	2 (5)

*Some symptoms could be present simultaneously.
ALS, amyotrophic lateral sclerosis; CDSUD, continuous deep sedation until death.

Table 2 Responses from palliative team

	PCU (n=23)	PCST (n=19)	Total (n=42)	P value
Responses				
Rejection	2 (9)	0	2 (5)	
Delay without CDSUD	10 (44)	8 (42)	18 (43)	
CDSUD	11 (47)	11 (58)	22 (52)	
Delay then CDSUD	7 (30)	6 (32)	13 (31)	
Immediate CDSUD (<72 hours)	4 (17)	5 (26)	9 (21)	
Average time of delay before CDSUD (in days)	11 (1–25)	5 (1–12)	8	0.06
Palliative care intervention				
Drugs adaptation	21 (91)	16 (84)	37 (88)	
Morphine	13 (57)	11 (58)	24 (57)	
Ketamine	3 (13)	2 (10)	5 (12)	
Methadone	0	1 (5)	1 (2)	
Neuroleptic	8 (35)	5 (26)	13 (31)	
Antidepressants	4 (17)	5 (26)	9 (21)	
Perimedullary analgesia/infiltration	1 (4)	1 (5)	2 (5)	
Midazolam at anxiolytic dose	17 (74)	9 (47)	26 (62)	
Intermittent sedation	1 (4)	2 (10)	3 (7)	
Psychosocial support	22 (96)	7 (37)	29 (69)	0.0001
Psychological support	20 (90)	9 (47)	29 (69)	
Volunteers' support	16 (70)	3 (16)	19 (45)	
Massages, body approach	16 (70)	3 (16)	19 (45)	
Hypnosis/relaxation	3 (13)	0	3 (7)	
Spiritual care	0	0	0	

CDSUD, continuous deep sedation until death; PCST, palliative care support team; PCU, palliative care unit.

/ relaxation / body care 45%). Increased palliative support was greater in PCUs than in PCSTs (p=0.0001) No spiritual support was recorded in the patients' files. In 26% of cases, family pressure appeared to be present during the initial or continued request for CDSUD.

The drugs used for CDSUD are described in table 3.

In all cases, midazolam was the drug used for CDSUD with an average dose required of 115 mg/24 hours (15–480). The initial average dose was 85 mg/24 hours (15–480), while the average dose on the last day was 152 mg/24 hours (17–480). A tachyphylaxis phenomenon, defined as the need to increase the

Table 3 Technique for CDSUD

	PCU (n=11)	PCST (n=11)	Total (n=22)	P value
Drugs used				
Dual therapy (midazolam+other drug)	7 (64)	4 (36)	11 (50)	
Midazolam	11 (100)	11 (100)	22 (100)	
Levomepromazine	3 (27)	0	3 (14)	
Hydroxyzine	3 (27)	0	3 (14)	
Diazepam	0	2 (18)	2 (9)	
Cyamemazine	0	1 (9)	1 (4)	
Dipotassium clorazepate	1 (9)	0	1 (4)	
Loxapine	0	1 (9)	1 (4)	
Dosage of midazolam (in mg/24 hours)				
Mean	83 (15–132)	147 (17–480)	115 (15–480)	0.21
Initial	39 (5–100)	132 (17–480)	85 (5–480)	0.01
Final	117 (20–288)	165 (17–480)	152 (17–480)	0.92
Tachyphylaxis	8 (73)	5 (46)	13 (59)	
Duration in days (mean, minimum, maximum)	3.2 (1–7)	2.5 (0.02–14)	3 (0.02–14)	0.15
Proportional sedation until death	6 (54)	1 (9)	7 (17)	0.07

CDSUD, continuous deep sedation until death; PCST, palliative care support team; PCU, palliative care unit.

midazolam doses to maintain the deep level of sedation, was observed in 13 (59%) of cases. In PCUs, significantly lower initial dosages were used than in PCSTs (39 vs 132 mg/day, p=0.01). Another drug was added in 11 (50%) cases, neuroleptic in 5 (22%), other benzodiazepine in 3 (14%) and antihistaminic in 3 (14%). CDSUD was maintained for an average of 3 days until death occurred. The life expectancy of patients under CDSUD was not significantly longer in PCUs (3.2 days) than in PCSTs (2.5 days) (p=0.15).

The life-threatening condition was considered to be 'short-term', that is, less than 15 days according to the French recommendations, for six (27%) patients when CDSUD was performed and for nine (50%) patients when CDSUD was not performed. The requests for CDSUD were analysed collegially for 25 (60%) patients.

DISCUSSION

The frequency of CDSUD requests made by patients followed by palliative teams in the Rhône-Alpes region is very low (0.5%) and the frequency of CDSUD is also lower (0.25%). The number of CDSUD requests is lower than the requests for euthanasia in the same area.[12] The frequency of CDSUD is also lower than in Denmark (2.5%), in Italy (8.5%) or in Flanders (15%), but in all settings (ie, whether or not in specialised palliative care beds)—and in these studies—CDSUD is not always performed at the patient's request.[9 13] The low rate of CDSUD in palliative care specialist services may be explained by the expertise in controlling symptoms and the psychosocial approach, and suggests that the rate of refractory symptoms needs to be compared with the expertise of the team in charge. These results need to be confirmed by a larger study.

According to our results, patients requesting CDSUD had 'serious and incurable' conditions, most of them with metastatic cancers. The number of patients with ALS is high, despite the low frequency of this disease. This could be related to the high level of distress in this disease,[14] with a high number of requests for euthanasia or physician-assisted suicide; in a prospective study, Maessen and colleagues find 31% of the requests relate to patients with ALS.[15 16]

Our study showed that 95% of patients had no spirituality documented. The lack of spiritual care at the end of life, particularly in PCUs, is surprising—as this need should be addressed and that in each hospital in France patients have access to a spiritual care adviser on request.[17] Our results suggest that in the palliative care services studied, spiritual needs are neglected and that more training is needed.

Our results highlight that one-third of the patients had an underlying major depressive state where the depression prevalence was estimated at 30%–70% of the cases.[18 19] Depression was not diagnosed and therefore undertreated in more than 50% of cases in the palliative and advanced phase,[20] and associated with higher symptom burden.[21] Despite the availability of many tools and recommendations,[22] the depression assessment was still neglected, whereas depression should be routinely assessed by screening tools in palliative care,[23 24] and should be mandatory in the case of requests for a CDSUD.

One trigger was present in more than one request out of two and seems to refer to a 'transient state of crisis'. The need to use a transitory and proportionate sedation adapted to this 'crisis situation', which by definition is not sustainable over time, is proposed in international recommendations.[5]

Our results underline that one to two patients express ambivalence in requests, including those with high-intensity requests. In this case, the request must be thoughtfully reassessed as suggested in recommendations.[25]

In our study, refractory suffering is found in almost all cases, mainly psychoexistential suffering (69%). Psychoexistential suffering as a refractory symptom is debated[5 26]; it is more difficult to define the refractoriness of this symptom.[27 28] However, despite optimised psychological and pharmacological management, psychoexistential suffering can persist and lead to requests for euthanasia or CDSUD.[10 29] Most recommendations suggest that intermittent sedation should be used before considering CDSUD.[5 30]

Our study shows that midazolam was the drug used for CDSUD as in other studies.[31] A tachyphylaxis phenomenon was observed in more than half of the cases, as described in the literature.[32] This suggests that midazolam should be used only for a short duration, or that another type of benzodiazepines, but with a longer half-life, should be used. In our study, the average dose of midazolam on the last day was higher than in other studies on palliative sedation; furthermore, the reason for palliative sedation is also different from that in other studies, where it used mostly to manage delirium or dyspnoea. Continuous sedation until death at the patient's request is obviously different from palliative sedation.

In our study, the average midazolam dose required to achieve deep sedation was higher in the PCSTs than in the PCUs. The difference could be explained by the fact that the palliative care physicians in the PCSTs are not prescribing, but only giving advice to other colleagues. We recorded that sometimes CDSUD was performed against the PCST's advice. The average midazolam dose was much higher than for usual palliative sedation use.[31 33] This result raises many questions, one of which being have midazolam doses increased to maintain the deep sedation, or to hasten death? This suggests that the doses of midazolam used in the last days could be an indicator to analyse the deep sedation practice, as the intention to proceed to such sedation is often hidden. As this is just a hypothesis, more large-scale studies are needed to determine whether there

is a link between the last doses of midazolam and the practice of clinical sedation.

When CDSUD was introduced, 'life-threatening' was deemed to be only a 'short period of time' (ie, less than 15 days) before death in only 29% of patients. But the prognostic assessment remains difficult despite the development of tools.[34] The studies conducted on this topic fail to identify clinical signs that combine both sensitivity and specificity for predicting the occurrence of death.[35] A multidisciplinary assessment is more accurate than an assessment by a caregiver alone, with an accuracy of 87.5% when survival is estimated in days.[36] This confirms the need of a multiprofessional assessment before the CDSUD, as requested in the legal framework. In our study, only two out of three applications for CDSUD benefited from a collegial decision. More training is needed so that healthcare professionals will keep within the legal framework.

In our study, deep sedation was maintained for an average of 3 days until death, as in the literature, which averaged 4 days. This may suggest that the CDSUD may have accelerated the occurrence of death in the cases where the survival of the patients was estimated to be more than 15 days. Although some studies demonstrate that CDSUD does not accelerate the occurrence of death[37] more studies are needed about the survival during the CDSUD.[38 39]

According to our results, the request for CDSUD occurs mostly following a request for euthanasia, and euthanasia is not legal in France. This suggests that CDSUD may be used as a substitute for euthanasia, even if the French law and the French recommendations state that CDSUD is not euthanasia. It seems that there is still a grey area between deep sedation and the practice of euthanasia even in countries where euthanasia is legal.[9] Despite many publications defining the concept, the topic is still controversial.[40]

Study limitations

The retrospective methodology is limited because of a lack of information on the medical records, which has created problems from the perspective of both research and legal aspects.

As the request for deep sedation is low, this study lacks power and more studies are needed with a larger number of patients. This study focused on specialised services, the results needs to be compared with those in other settings.

CONCLUSION

The new French law allowing the patient to have a CDSUD at his/her request raises questions in palliative care practice, as the same word—sedation—is used to describe a different practice. This study shows that, even in specialised units, the legal and ethical issues need to be addressed, especially the short-term prognosis and the collegial decision. Patients request CDSUD mostly after a request for euthanasia, which raises ethical issues, especially if the sedation is not proportional to the degree of suffering, or in case of existential distress.

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