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Nationwide Study of Continuous Deep Sedation Practices Among Pediatric Palliative Care Teams

Running title: End of Life Sedation in Pediatric Palliative Care

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Abstract

Context: Palliative sedation practices evolved in France when the Claeys-Leonetti law passed in 2016 authorized patient-requested continuous deep sedation (CDS) until death. Its implementation in the pediatric setting is less frequently encountered and can pose several clinical and ethical challenges for healthcare teams and families.

Objectives: Our study aimed to describe CDS requests and practices of patients receiving specialized pediatric palliative care in France since its legalization in 2016.

Methods: We conducted a nationwide multicentric, descriptive, retrospective study using a self-report questionnaire completed by all Pediatric Palliative Care (PPC) Teams that were involved in a CDS case between January 2017 and December 2019.

Results: Six PPC teams had cared for six patients that had requested CDS, predominantly male adolescents/young adults diagnosed with a solid tumour. The refractory symptoms were diverse (pain, bleeding, sensory loss) and always coupled with psycho-existential suffering. Each request was analyzed in multidisciplinary collegial meetings. Parental consent was always obtained regardless of age. Sedation typically required the use of multiple drugs including Midazolam (n=5 cases), Chlorpromazine (n=3), Ketamine (n=2) and Propofol (n=2). Despite close monitoring, achieving a satisfactory level of deep sedation was challenging and most patients unexpectedly awoke during CDS. Death occurred between 27 and 96 hours after induction.

Conclusion: Managing patient-requested CDS in pediatrics is challenging due to its rarity, multi-factorial refractory symptoms and drug tolerance despite polytherapy. Few recommendations exist to guide CDS practice for pediatricians. Further studies investigating pediatric CDS practices across various cultural and legal settings, refractory symptom management and specific pharmacology are warranted.

Keywords: Continuous Deep Sedation, Palliative Care, Pediatrics, Decision Making, Benzodiazepines

Key statement: This article describes a nationwide descriptive study of continuous deep sedation (CDS) until death practices within the pediatric setting. The results indicate that CDS remains rare among this age group and poses challenges of complex refractory symptom management and tachyphylaxis despite polytherapy.

Introduction

Palliative sedation is an increasingly common practice in end-of-life care. The legal and ethical framework regulating its clinical practice, however, can vary between countries (1–4). Palliative sedation, as defined by the European Association for Palliative Care (EAPC) and the French Health Authority (*Haute Autorité de Santé*), is the monitored use of sedative

drugs to induce a state of reduced consciousness in order to relieve the patient's perception of otherwise unbearable suffering (5)(6). Sedation is most often employed when all other therapeutic means have failed to alleviate a refractory symptom (5). French medical practice guidelines distinguish two types of palliative sedation: proportional sedation and deep continuous sedation. Proportional sedation is potentially reversible. The degree of decreased consciousness is variably adjusted from a Richmond Agitation-Sedation Score of -1 to -5 until symptom relief is attained, hence its name. Continuous deep sedation (CDS) seeks a profound, unresponsive unconscious state corresponding to a Rudkin score of 4-5 or a Richmond Agitation-Sedation Scale score of -4 or -5 which is maintained until death (see appendix for sedation monitoring scores)(5).

Deaths under the age of 25 represent about 1% of the France's deaths each year (or approximately 6500 children and young adults) (7). Palliative CDS at the patient's request became legal in France under the Claeys-Leonetti law in 2016 (8). CDS is authorized under two circumstances: management of refractory symptoms at the end of life and preventive management of symptoms secondary to withdrawing life-sustaining treatment (5). For patients suffering from refractory symptoms, their condition must be severe and incurable, with an estimated life-expectancy of less than two weeks (9). All CDS requests are examined collegially and the opinion of at least one external consulting physician without any hierarchical relationship to the medical team is required (8). Medical guidelines recommend inducing with a Midazolam titration until an unresponsive unconscious state is obtained. Neuroleptic agents can be co-administered as second-line, and Ketamine or Propofol as third-line sedatives if necessary. The patient is regularly monitored to ensure deep unconsciousness (Rudkin 5 or RASS -5), symptom relief and freedom from side effects (5). During CDS, French law requires any life-sustaining therapies such as intravenous or enteral hydration and feeding should be stopped. However, if the patient and/or family opposes for psychological or cultural reasons despite being informed of potential adverse effects (increased bronchial secretions, oedema, etc.), clinical guidelines allow for minimal hydration to be continued (approximately 250mL/24h for adult patients) (5). Analgesia and any relevant symptomatic treatment should continue (5). It is important to note that at the time of our study, euthanasia was not legally permissible in France.

CDS is equally authorized for minors and the procedure is overall the same as for adults with a few specifications regarding discernment and informed consent. Although minors may request CDS directly themselves, their parents' and/or legal guardian's consent should be obtained. Assessment of the minor patient's faculties of understanding, discernment

and autonomy via psychological and/or psychiatric evaluation is recommended. If time allows, this evaluation should be repeated, although this timeframe is not specified by the law as it must take into account individual circumstances. Sedation guidelines are the same as for adult patients: coma induction by Midazolam titration and co-administration of second or third-line sedative drugs if necessary to obtain a satisfactory level of unconsciousness (5,10).

CDS is less frequently encountered in the pediatric setting than in adult medicine and can pose several clinical and ethical challenges for healthcare teams and families that may be specific to this age group. Scientific literature is equally scarce and evidence-based pediatric-specific sedation protocols lacking. Our study aimed to describe CDS requests and practices of patients receiving specialised pediatric palliative care in France since its legalization in 2016.

Materials and Methods

We conducted a multicentric, nationwide, observational, cross-sectional study. All pediatric palliative care (PPC) teams across France were first informed of the study in June of 2017 via the French Society of Pediatric Palliative Care to which all French PPC teams are affiliated. All teams that reported having participated in a CDS between January of 2017 and December of 2019 were sent a questionnaire to be completed by the PPC team and returned by mail. The questionnaire consisted of 35 closed-ended questions, 2 open-ended questions and a space for writing optional free-form commentaries. The questions covered the following topics: medical history, patient's CDS request, decision-making process, clinical characteristics of the procedure, and post-mortem follow-up. Any pediatric palliative care team caring for a terminally ill patient, regardless of age, who requested CDS between January 2017 and December 2019 was included. As PPC teams coordinate care across all settings of their attributed geographical region, all CDS cases were included regardless of location (hospital or home). As our study focuses on mature pediatric patients requesting CDS for refractory symptoms, other forms of palliative sedation (intermittent and emergency palliative sedation) were not included in this study. Medical records were used by the PPC teams to extract any necessary information. Patients and their parents/legal guardians were informed of the study and none opposed the use of their medical records. All patients remained anonymous on questionnaires. If there was any missing data on questionnaires, teams were contacted directly to complete data where possible. All French pediatric CDS cases during the study period were included in this study, and due to the small sample size no statistical analysis was performed. This study was approved by the local research committee

of Strasbourg University Hospital. The study was conducted and reported according to STROBE guidelines for cross-sectional studies (11).

Results

Among all 24 French PPC teams, six had received a request for CDS from six patients between 2017 and 2019. All young people in our study who requested CDS were accepted. No request was denied, but one patient changed their mind after psychological evaluation. Requests came predominantly from Adolescent and Young Adult (AYA) oncology departments (5 cases out of 6) and all oncology patients had solid tumours. One request came from pediatric nephrology. Two-thirds of patients were over 18 years of age (n=4 cases) and male (n=4). Table 1 below describes patient characteristics.

Table 1: Patient characteristics

The CDS request

Most patients formulated their request themselves (n=4 cases), but two patients voiced their request via their parents. Even though some patients were legally of age, parents were always consulted as they were hospitalized on a pediatric ward. All parents consented: two-thirds were immediately in accord (n=4: cases 3-6) and one-third (n=2: cases 1 and 2) needed more time and explanations to come to terms with their child's request. For the latter, the leading reasons for this were linked to the emotional difficulty of accepting the impending death of their child and losing the possibility of interacting with them after sedation initiation. Patients were informed of the possibility of CDS either from the media (n=1), from their parents (n=1), from their oncology or nephrology team (n=2) or from their PPC team (n=2). The time lapsed between gathering information and requesting CDS varied from < 2 weeks (n=1), 2-4 weeks (n=2) and >4 weeks (n=3). Three patients had previously requested or inquired about euthanasia prior to formulating a CDS request. All CDS requests were linked to refractory symptoms, mainly pain (n=3), but also sensory loss (n=1), bleeding (n=1), and renal failure associated with multiple thrombosis due to transplant rejection (n=1). In addition to physical symptoms, all patients expressed some degree of psycho-existential suffering. Of the six patients requesting CDS, four were evaluated by either a psychologist or psychiatrist (cases #2, 4, 5, 6). After psychological evaluation, one patient retracted their request (case #6). This patient had been first informed of CDS via the internet and media. After discussing CDS with health care professionals and what it would entail for him, he chose to retract his request.

The decision-making process

The five remaining CDS requests (cases #1-5) were discussed collegially with the help of an outside third-party consultant. The participants of these collegial meetings were: referring doctors (n=5 cases), pediatric palliative care team (n=5), nursing staff (n=4), residents (n=4), and mental health professionals (psychologists, psychiatrists) (n=3), and third-party physicians (adult palliative care physician (n=3), home hospice care physician (n=2), and/or clinical ethics unit (n=2)). These meetings typically lasted one hour. The request was considered “clear” and the patient considered to have a “predicted survival of < 2 weeks” in 4 of 5 cases. For case #1 in which the request was not considered “clear”, the patient was in home care and the pediatric palliative care team did not directly meet the patient. In only one case was the patient on life-sustaining treatment (daily platelet and red blood cell transfusion). After debate, all requests were eventually unanimously accepted by staff attending the meetings (n=5). Although consensus is not a requirement of the law *per se*, the participating teams actively sought it by the means of these interdisciplinary discussions, repeating them if necessary. For two cases, multiple meetings were needed to reach a decision. These meetings were reconvened for the following reasons: the predicted survival was greater than two weeks (case #4) and more time was necessary to address the staff’s multiple questions and concerns as meetings were typically limited to one hour (case #2). Most nursing staff on the ward (n=4 cases) consented easily to the patient’s request except for one case (case #3) where the nurses felt pressured to respond hastily. On the contrary, the medical staff, who are legally held responsible for the formal decision-making, found it harder to consent (n=4, cases #2-5). The reported difficulties stemmed from the novelty of the request, strong bond between the staff and the family, and perceived responsibility of staff in making the decision.

Sedation protocol and procedure

Four CDS took place at the hospital (cases #2-5) and one at home (case #1). Before commencing the CDS, two patients asked to have a last bite to eat (cases 2 and 5), and one patient asked for the nurses he knew best to be present (case #5). Four patients received an anti-anxiety treatment by intravenous Midazolam.

For the sedation itself, all teams (n=5 cases) used Midazolam in association with another sedative drug (table 2): Ketamine (n=2), Chlorpromazine (n=3), and Propofol (n=2). These second-line drugs were initiated if necessary to obtain a level of sedation corresponding to Richmond Agitation Sedation Scale -4. In three cases, Midazolam was initially titrated

until satisfactory sedation was reached. For the other two cases, either Midazolam that had already been introduced at low dosage for anxiety was doubled (case #1) or was initiated empirically at 0.06mg/kg/h (case #3). Minimal intravenous hydration was continued in three cases (n=3) between 240ml/day (cases #3-4) and 480 mL/day (case #5), predominantly to help keep central catheters open and functional. All artificial nutrition was discontinued (intravenous feeding for case #4). Analgesia was continued in all cases. Two patients had intravenous Morphine (0.15-0.3mg/kg/h) and two patients had intravenous Oxycodone (0.34-0.36 mg/kg/h). Other co-analgesia included: Ketamine (1-2mg/kg/d), Amitriptyline, Corticosteroids and Acetaminophen. The level of sedation was monitored using either the Rudkin-Score (n=2) or the Richmond Agitation Sedation Scale (n=2). One team did not use any score to monitor sedation (case #4), one team used their score only for the first 6 hours (case #3), and one team admitted to using their score only sporadically and did not report it in the patient's records (case #1). In most cases (n=4: cases #1, 3-5) the patients woke completely at least once during the CDS, requiring pharmaceutical adjustment of sedative drugs. In three cases (cases #1,3,4) the unexpected awakening was agitated and the child sought reassurance. The sedation drugs were quickly adjusted and the awakening lasted only a matter of minutes. In one case (case #5) it was calm and the patient was able to talk to his mother. Sedation was increased after almost one hour of being awake. In all cases, health care professionals managed monitoring and adjustments to sedation therapies, and no therapeutic intervention was expected of parents. Death occurred <24h after induction for one patient, between 24-48 hours for two patients and between 48-96 hours for two patients (average of 2.4 days or 57 hours).

Table 2: Sedative Drugs

For two teams they felt that the CDS went smoothly (cases #2 and 3), however the other three teams experienced difficulty in achieving a satisfactory level of sedation. In all cases, the families seemed calm and reassured despite occasional moments of impatience, according to the ward's medical staff. Following the death, bereavement follow-up was offered and accepted by four families (cases #2-5). A debriefing session was offered for four of the medical teams (cases #1,2,4,5). An overview of each patient's case and sedation protocol can be seen in Table 3.

Discussion

Since the enactment of the French Claeys-Leonetti Law in 2016 authorizing patients to request CDS, six young people under PPC, predominantly male adolescents and young adults diagnosed with a solid tumour, voiced their desire to be deeply sedated at the end of their life. The refractory symptoms were diverse (pain, bleeding, sensory loss) but always coupled with psycho-existential suffering. Each request was analysed in multidisciplinary collegial meetings and repeated discussion was often necessary to reach a decision. Patient and family consent was always obtained. Sedation typically required the use of multiple drugs including Midazolam, Chlorpromazine, Ketamine and Propofol. Despite close monitoring, achieving a satisfactory level of deep sedation proved to be challenging and most patients unexpectedly awoke during CDS. Death occurred within 96 hours following induction.

Palliative sedation therapy can vary considerably internationally in regards to definition, indications, drug selection and dosage, clinical guidelines and legal framework (2–4). Our study specifically focused on terminally ill pediatric patients suffering from refractory symptoms who requested deep continuous palliative sedation rendering them unconscious until death. In European literature, the prevalence of CDS ranges from 2.5-8.5% of all deaths (12) and is on the rise with more recent statistics estimating up to 15-20% of adult deaths (13–15). However, these statistics include all scenarios of CDS: those with intact decision making capacity who had uncontrollable suffering (as in our study), but also those who requested withdrawal of life-sustaining treatment, those who were unable to make or execute decisions themselves, or other undefined scenarios. In any case, sedation performed upon patient request remains a minority, estimated at 15-16% of all CDS practices (15,16). Literature on the pediatric population is scarce and few studies have explored CDS practices in children, adolescents and young adults. Our small study sample highlights that patient-requested CDS is rare among this age group. The under 25 age group (approximately 20 million) counts for nearly one third of France's overall population (about 67 million) (17). Approximately 6500 young people under the age of 25 die each year in France, representing 1% of the country's deaths (7). In line with international guidelines, only in exceptional circumstances is CDS employed from the initiation of palliative sedation therapy (1). In other studies, most decisions to use CDS were made without the involvement of the pediatric patient (18,19) but parental consent was often sought (18–20). This could possibly be explained if the sedation was primarily used to prevent onset of intolerable suffering during withdrawal of life-sustaining treatment or because the child was unable to communicate (coma, mentally handicapped, etc.). Furthermore, our population was considerably older (teenagers and young

adults) in relation to other pediatric studies where the average age was <12 years (18,19). This can be explained by the fact that we included only patients capable of clearly, autonomously and maturely expressing their desire to be sedated, as required by French legislation (5,8). All patients in our study requested and consented to CDS, and the reasons for not seeking a minor patient's consent requires further investigation. We assume that if the minor's consent was not sought, the patient was too ill to communicate at that time. However, the context in which CDS is initiated merits explanation to better understand these situations.

The French Claeys-Leonetti law authorizes any person, regardless of age, to request CDS in certain end-of-life circumstances. Notifying young patients of their legal rights can seem awkward or difficult for some health care professionals. Our experience shows that they can be informed of the possibility of CDS without it necessarily triggering hasty decision-making. Almost all patients took at least two weeks to formulate a request after having been informed of the possibility of CDS. It is preferable to discuss CDS outside of stressful contexts when it has been announced that there are no further disease directed therapies. Furthermore, it is important that dialogue be established on trust and in tune with the young patient's maturity, fears and needs. It also seems to us that maturity and the quality of the patient-carer relationship are the deciding factors for informing patients of their legal rights to sedation rather than age. In our study, when CDS was requested it was always granted and initiated by the medical team within 3-12 days of the request. This time frame seems to align with CDS requested by adults in which initiation was delayed on average 12 days (21). However, in the adult population requests have reported to be rejected, or rendered unnecessary after attempting better symptom management and reinforcing psychological care (21). The "right timing" is difficult to discern and impossible to ascertain. Although the law requires a short predicted survival time, medicine alone is incapable of correctly predicting with certainty a patient's life span. Despite this, most patients passed within two weeks of formulating a request, reflecting that their request was formulated towards the end of life. Furthermore, studies show that the evaluation in performance status and symptom burden is often out of sync between children, clinicians and caregivers (22,23). In our study, time was sometimes necessary for both families and health care professionals to come into agreement. It is important to respect the different temporalities at play when discerning CDS: that of the patient and their illness, the family and the healthcare professionals.

In concordance with both pediatric and adult literature, cancer was the predominant primary diagnosis and the patients were more often male (12,14,18,21). The most common refractory symptoms resorting to CDS described in literature are: psycho-existential distress,

pain, dyspnoea, delirium, nausea/vomiting/occlusion, seizures and bleeding (3,18,21,24). Our sample consistently found psycho-existential distress associated with physical symptoms (mainly pain). As our study focused on CDS and not intermittent nor emergency palliative sedation, this could explain why common symptoms such as dyspnoea and delirium were not found among our sample. Despite the prevalence of psycho-existential suffering, not all patients benefited from a psychological evaluation nor received anti-anxiety treatment. As there is no published literature to date exploring refractory psycho-existential distress leading to CDS among the pediatric population, this could reflect a significant lack of awareness, screening and management of such symptoms at the end of life in this specific age group. One request was retracted after psychological assessment demonstrating the impact of mental health care on this patient's decision-making. Among adult patients requesting CDS, reinforcement of psychological care was offered in 69% per cent of cases, and 43% of requests were not reiterated (21). Our study highlights that pediatric patients requesting CDS are confronted with a "total pain" (25) combining physical and psycho-existential symptoms that need to be addressed, regardless of age. Following up psychological evaluation with reinforced mental health care is an essential element of CDS procedures.

Contrary to adult literature in which collegial discussion of CDS requests ranges from 60-90% (16,21), all of our cases were analysed collegially as mandated by French law. As there can be a gap between what is legally desired and the clinical reality, it is important to emphasize that collegiality was constantly upheld in pediatrics. Multidisciplinary and third-party input were essential for the decision-making process in the pediatric setting. As CDS cases are rare and often generate ethical tension, creating space for discussion helps expose and converge viewpoints and practices as well as share the decision-making process. Although illegal in France as of 2021, half of the patients had previously requested euthanasia prior to CDS, a tendency also found among the adult population (21). As euthanasia becomes more present in society and media, it can be expected that such requests will increase with time, even among children and teenagers. Distinguishing CDS from euthanasia can be confusing for families and health care professionals alike. Much of the definitional difference stems from the underlying intention (26). The intention of CDS is to relieve intolerable suffering by reducing consciousness, and the sedative drug is a means of symptom control. Death occurs due to the natural evolution of the underlying disease. In some circumstances, the double effect of sedative drugs, although not intended, is tolerated. On the other hand, euthanasia aims to directly end a patient's life by administering a lethal drug (26,27). As the boundary between CDS and euthanasia can be confusing, discussing each CDS request within

multidisciplinary collegial meetings is of invaluable support to health care professionals confronted with evaluating difficult end-of-life situations and making decisions in a context of intense suffering.

In our study sedation typically required the use of multiple drugs. Once CDS was decided, sedation was induced using Midazolam in all cases, mainly via titration. However, maximum Midazolam doses were up to triple recommended adult doses (6,16,21,28). Pediatric dosing is often extrapolated from adult pharmacokinetic studies; however there can be significant variation in pharmacokinetic properties among age groups and even among individuals (29–31). A recent review of inter-individual midazolam clearance variation in children demonstrated that there is a reported 2.0-fold to 5-fold variation in clearance values among critically ill children and adolescents under mechanical ventilation (29). This could be attributed to various factors (systemic inflammatory responses, age-related cytochrome activity for midazolam metabolism, weight, etc.)(29–31), and could potentially help explain the large dosing ranges among our population. Furthermore, opioid-tolerant patients often require significantly higher dosages than naïve patients for similar results in terms of pain management (32,33). One study reports up to 5–6 fold higher opioid consumption in order to achieve an adequate analgesic response (33). Similarly, longer administration periods of Midazolam are also significantly correlated with escalating doses (34). Most of our patients had previous exposure to opioids or benzodiazepines which could contribute to the large doses reported in our study.

Contrary to adult CDS cases where benzodiazepines combined with opioids were generally sufficient for over half of patients (15,16,21), polytherapy was almost always necessary to achieve a satisfactory level of unconsciousness and opioids were only continued as analgesics and never as sedatives. The other drugs used were Chlorpromazine as second-line sedatives, and Ketamine and/or Propofol as third-line. Neuroleptics such as Levomepromazine have demonstrated efficacy for difficult sedation in the pediatric intensive care unit (35). Over 20mg/h of Midazolam, it is considered that little or no additional therapeutic effect is obtained and adding second-line sedative medications is recommended beyond this threshold (36). Adding a neuroleptic over a threshold of 20mg/h of Midazolam could improve sedation quality. Propofol remains a last resort due to its potential hemodynamic and respiratory depression, but can be an effective comfort measure for pediatric palliative sedation when needed (37,38). The PPC teams, who were confronted with their first and only CDS case during the study period, faced the additional difficulty of lacking scientific literature specifying medication dosing in pediatric palliative CDS on which to

found and compare their clinical experience. Our article is the first to report specific dosing in this context, and other multicentric studies reporting their pediatric CDS protocols would be helpful for comparison.

The only reported adverse effect of our CDS cases was a tachyphylaxis (rapidly diminishing response to successive doses of a drug rendering it less effective) and subsequent alertness often taking family members and health care professionals by surprise. Abrupt awakening during sedation is not described in literature and is perhaps more prevalent in the pediatric population. Most of the awakenings were agitated requiring rapid adjustment of sedation drugs. Insufficient clinical monitoring and missing early warning signs could have contributed to these awakenings. As CDS is a rare practice in pediatrics, some professionals might not have been aware of possible tachyphylaxis and assumed that the patient would remain deeply sedated without needing further monitoring or adaptation of drugs over time. For the patient whose awakening was calm and allowed for conversation, a proportional sedation could have perhaps sufficed and the indication of CDS in this case could be called into question. In any case, pre-warning families and caregivers that such events are possible, close monitoring, and anticipating therapy adjustments in the sedation protocol for rapid reaction are helpful points for CDS to proceed smoothly. Pharmacological studies for this specific age group are warranted to improve sedation protocols and titration regimens.

Our study has some limitations. Our sample size, although it includes all CDS requests managed by PPC teams in France during the study period, is very small. Furthermore, cases 3-6 were young adults and not strictly “pediatric” patients (<18 years). Added to the lack of literature on patient-requested CDS in pediatrics for comparison, we are unable to conclude whether our results are representative of the pediatric population in general. Furthermore, legal framework and clinical guidelines regulating palliative sedation practices can vary considerably between countries. Results should thus be extrapolated with caution especially to other age groups (younger children) and cultural contexts. Finally, this present retrospective and descriptive questionnaire-based study cannot explore in depth the family and staff’s experience of CDS and ethical concerns. Qualitative studies are underway to further investigate these aspects.

Conclusion

In conclusion, managing patient-requested CDS in pediatrics is challenging due to its rarity, multi-factorial refractory symptoms and tachyphylaxis despite polytherapy. Few recommendations exist to guide CDS practices for pediatricians, and its usage among young

patients raises many questions. Our study was the first to provide data concerning this specific type of palliative sedation among patients treated by pediatric teams, and significant issues concerning distinguishing CDS from euthanasia and inadequate drugs regimens need to be addressed. Further studies investigating CDS practice in pediatrics across various cultural and legal settings, management of refractory symptoms especially psycho-existential distress, and pediatric-specific sedation pharmacology are warranted.

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Conflicts of interest

The authors declare that there is no conflict of interest.

Author contributions

AR conducted the study and drafted the article for publication. EVC conducted the study, edited all drafts of the manuscript and approved the final version of the manuscript.

GR, FJJ, CL, MLV and SF participated in the study, edited all drafts of the manuscript and approved the final version of the manuscript. NC oversaw the conception of the review design and the research procedure, edited all drafts of the manuscript and approved the final version of the manuscript.

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Table 1: Patient characteristics

Patient	Gender	Age (years)	Diagnosis
1	Female	12	Ewing's sarcoma stage IV, diagnosed at 10 years of age.
2	Male	17	Chronic kidney failure, diagnosed at 3 years of age and kidney transplant rejection at 14 years of age.
3	Female	19	Ewing's sarcoma stage IV, diagnosed at 15 years of age.
4	Male	19	Alveolar Rhabdomyosarcoma stage IV, diagnosed at 17 years of age.
5	Male	21	Neuroblastoma stage IV, diagnosed at 3 years and relapse at 18 years.

6	Male	23	Alveolar Rhabdomyosarcoma stage IV, diagnosed at 20 years of age.
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Table 2: Sedative Drugs

Drug	Starting Dose		Maximal Dose	
	In mg/kg/h	In mg/h	In mg/kg/h	In mg/h
Midazolam	0.04-0.47 (mean=0.15)	2.0-28.0 (m=7.6)	0.12-1.2 (m=0.6)	5.0-74.0 (m=28.2)
Chlorpromazine	0.01-0.04 (m=0.02)	0.5-2.0 (m=1.17)	0.01-0.08 (m=0.06)	1.0-4.0 (m=3.0)
Ketamine	0.02-1.0 (m=0.51)	1.0-60.0 (m=30.5)	0.6-2.0 (m=1.3)	30.0-120.0 (m=75.0)
Propofol	1.0-1.5 (m=1.25)	60.0-75.0 (m=67.5)	3.0-5.0 (m=4.0)	150.0-180.0 (m=165.0)

Patient (Weight in kilos)	Refractory symptoms	CDS request	Time lapsed until CDS request	Time lapsed between CDS request and induction	Sedative drugs (Starting- maximal dosage)	Analgesia	Adverse Effects	Death
1 (30 kg)	Refractory pain from multiple metastases. Psychologic al suffering and inquired about euthanasia.	Requested by: patient herself Source of info: Media and PPC team	2-4 weeks	12 days	Midazolam (0.1-0.83 mg/kg/h) Chlorpromazi ne (0.03 mg/kg/h)	Morphine	Periods of consciousne ss	3 days (60h)
2 (40 kg)	Kidney transplant rejection, no possibility of 2 nd transplant nor dialysis due to multiple thrombosis. Psychologic al suffering from lack of treatment possibilities	Requested by: patient himself Source of info: Nephrolo gy and PPC teams	2-4 weeks	About 3 weeks, 3 collegial discussio ns were necessary to reach consensu s	Midazolam (0.05-0.125 mg/kg/h)	No analgesia necessary	No reported adverse effects	2 days (32h)
3 (50 kg)	Loss of sight and hearing from multiple	Requested by: parents Source of	> 4 weeks	6 days (5 days between request and	Midazolam (0.6 mg/kg/h) Chlorpromazi ne (0.24-1.92	Oxycodone Amitriptyline Ketamine Acetaminoph en	Periods of consciousne ss	4 days (96h)

	metastases. Psychological suffering and previous request for euthanasia.	info: Oncology team		collegial decision, induction the following day)	<i>mg/kg/h</i>) Propofol (1.5-3 <i>mg/kg/h</i>)			
4 (50 kg)	Refractory pain from multiple metastases. Psychological suffering.	Requested by: parents Source of info: Oncology team	< 2 weeks	1 month, 2 collegial discussions were necessary to reach consensus	Midazolam (0.04-0.12 <i>mg/kg/h</i>) Ketamine (0.02-0.6 <i>mg/kg/h</i>) Chlorpromazine (0.04-0.08 <i>mg/kg/h</i>)	Oxycodone Corticosteroids	Periods of consciousness	3 days (72h)
5 (61 kg)	Refractory epistaxis from facial bone metastasis and refractory thrombopenia. Psychological suffering with previous request for euthanasia.	Requested by: patient himself Source of info: PPC team	> 4 weeks	3 days (2 days between request and collegial decision, induction the following day)	Midazolam (0.47-1.2 <i>mg/kg/h</i>) Ketamine (1-2 <i>mg/kg/h</i>) Propofol (1-3 <i>mg/kg/h</i>)	Morphine	Periods of consciousness	2 days (27h)
6 (60 kg)	Refractory pain from multiple metastasis. Psychological suffering.	Requested by: patient himself Source of info: Media	> 4 weeks	Retracted CDS request	N/A	N/A	N/A	N/A

Table 3: Case characteristics and CDS protocol

Appendix: Sedation monitoring

Richmond Agitation-Sedation Score

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony

+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unroutable	No response to voice or physical stimulation

Source: Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002 Nov 15;166(10):1338-44. doi: 10.1164/rccm.2107138. PMID: 12421743.

Rudkin Score

Score	Description
1	Fully awake
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation
5	Eyes closed and unroutable to mild physical stimulation

Source: Rudkin GE, Osborne GA, Finn BP, Jarvis DA, Vickers D. Intra-operative patient-controlled sedation. Comparison of patient-controlled propofol with patient-controlled midazolam. *Anaesthesia.* 1992 May;47(5):376-81. doi: 10.1111/j.1365-2044.1992.tb02216.x. PMID: 1599059.