Pediatric Palliative Sedation Therapy with Propofol: Recommendations Based on Experience in Children with Terminal Cancer

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Abstract

Background: The use of propofol for palliative sedation of children is not well documented.

Objective: Here we describe our experience with the use of propofol palliative sedation therapy (PST) to alleviate intractable end-of-life suffering in three pediatric oncology patients, and propose an algorithm for the selection of such candidates for PST.

Patients and Methods: We identified inpatients who had received propofol PST within 20 days of death at our institution between 2003 and 2010. Their medical records were reviewed for indicators of pain, suffering, and sedation from 48 hours before PST to the time of death. We also tabulated consumption of opioids and other symptom management medications, pain scores, and adverse events of propofol, and reviewed clinical notes for descriptors of suffering and/or palliation.

Results: Three of 192 (1.6%) inpatients (aged 6–15 years) received propofol PST at the end of life. Consumption of opioids and other supportive medications decreased during PST in two cases. In the third case, pain scores remained high and sedation was the only effective comfort measure. Clinical notes suggested improved comfort and rest in all patients. Propofol infusions were continued until the time of death.

Conclusions: Our experience demonstrates that propofol PST is a useful palliative option for pediatric patients experiencing intractable suffering at the end of life. We describe an algorithm that can be used to identify such children who are candidates for PST.

Introduction

THE TERM “PALLIATIVE SEDATION THERAPY” (PST) was recommended by Morita et al. to supersede the phrase “terminal sedation,” which may be confused with euthanasia in patients approaching the end of life; the primary clinical aim of PST is relief of distress.¹ Ethical review has suggested that PST be reserved for patients experiencing severe suffering refractory to standard management at the end of life.² Therefore, clinicians considering this option must first determine that other interventions provide inadequate relief, provide intolerably delayed relief, and/or cause intolerable morbidity.^{3,4}

Cancer patients often experience pain at the end of life. If intravenous morphine does not provide adequate relief, dose escalation and/or opioid rotation may be effective.⁵ Anxiety, restlessness, and delirium may be treated with sedatives, most commonly benzodiazepines (lorazepam and midazolam) in adults^{3,4} and children.⁵ When these standard regimens do not

relieve symptoms, the anesthetic propofol may be a useful adjuvant in adults^{6–11} and children.^{12–15}

Propofol is commonly used for induction of anesthesia because of its rapid, smooth onset of action. Continuous propofol infusion provides titratable levels of sedation,^{16,17} and is reported to successfully relieve suffering at the end of life in adults.^{6–11} However, there is limited information regarding the use of propofol for end-of-life PST in children.^{12–14}

Here we describe our experience in using propofol PST in three pediatric cancer patients at the end of life. On the basis of this experience and a review of the literature, we propose an algorithm for use in identifying pediatric candidates for PST, and specifically for the selection of propofol as a sedation agent.

Methods

The St. Jude Children’s Research Hospital Institutional Review Board approved this retrospective review. St. Jude is

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a 60-bed tertiary-care institution for children with life-threatening diseases. Patients range in age from newborns to young adults.

We reviewed pharmacy records from January 2003 to May 2010 to identify all inpatients treated with propofol for control of intractable symptoms during their last 20 days of life. Cases in whom sedation was used to facilitate intubation or other procedures were excluded. We analyzed the details of the patients who received PST with propofol.

Data collected included age, sex, primary oncologic diagnosis, indications for propofol use, pain scores (when patients were awake), and patient symptoms, as well as opioid, benzodiazepine, and propofol dose regimens before and during propofol sedation. Opioid dosages were calculated as intravenous morphine equivalent (ME) dosages (mg/kg/h) on the basis of opioid equianalgesic potency, using the following ratios: fentanyl:morphine, 100:1; hydromorphone:morphine, 5:1; and sufentanil:morphine, 1000:1. Opioids and benzodiazepines were given as continuous infusions, boost doses, and clinician-administered boluses. Pain intensity scores and sedation status, categorized as awake versus asleep (unconscious or insufficiently alert to respond to pain assessment), were obtained for a period starting 48 hours before initiation of propofol, and ending at death. Pain was assessed at least every 4 hours while patients were awake, and 1 hour after any pain intervention by using age-appropriate pain assessment tools (the Wong-Baker FACES pain scale¹⁸ for patients ages 4–7 years, and the numerical rating scale¹⁹ for those older than 7 years). Other indicators of symptom control included clinicians' progress notes and patient/caregiver comments recorded in these notes.

Results

Between 2003 and 2010, 3 of 192 (1.6%) children who died as inpatients received PST with propofol for intractable pain, anxiety, and/or agitation, refractory to standard measures of palliation. Demographic data are provided in Table 1. The opioid, benzodiazepine, and propofol dose regimens of the respective patients are presented in Figures 1, 2, and 3. Pain scores and sedation status are shown in Table 2.

Case reports

Case 1. A 9-year-old boy had metastatic angiosarcoma of the spleen, severe abdominal pain caused by the primary

tumor, and generalized pain caused by bone metastases. Pain, agitation, and anxiety were incompletely controlled by high doses of fentanyl (subsequently sufentanil), midazolam, and dexmedetomidine, as reflected by frequent adjustment of the basal and demand settings of the fentanyl patient-controlled analgesia (PCA), numerous clinician boluses, and boost demands far exceeding delivered doses. Opioid consumption increased significantly during the 24 hours before initiation of propofol, from 15 to 29.4 mg/kg/h ME (Fig. 1). A case conference and ethics consult concluded that propofol sedation was indicated to relieve uncontrollable severe pain and refractory suffering, and an infusion was started at 30 mcg/kg/min (1.8 mg/kg/h). The infusion was briefly discontinued on day 6, due to the potential risk of propofol infusion syndrome with prolonged infusions, and again on day 7, in response to the mother's request to interact with the child. Each time, the opioid and benzodiazepine infusions were supplemented with clinician boluses to compensate for discontinuation of propofol, but resumption of propofol was necessary within a few hours by evidence of suffering, described as "whimpering" and "screaming in pain." On day 8 of propofol sedation, total parenteral nutrition was discontinued and the mother agreed to a do not attempt resuscitation (DNAR) order. The child was reported to be "very comfortable," with the notation "breathing is close to agonal." The patient remained on propofol infusion for 9 days, until the time of death.

Case 2. A 6-year-old boy had progressive neuroblastoma and secondary diagnoses of hypertension, posterior reversible encephalopathy syndrome, renal insufficiency, hyperbilirubinemia, gram-negative and staphylococcal bacteremia, and disseminated *Candida tropicalis* infection. He was experiencing abdominal pain, nausea, vomiting, and hallucinations, despite sufentanil PCA, lorazepam, ondansetron, and haloperidol. An epidural catheter had been inserted approximately 1 month previously in an effort to control abdominal pain. During the 24 hours before the start of PST, opioid consumption increased from 8.6 to 35.2 mg/kg/h ME, and PCA demands exceeded the doses received (Fig. 2). The patient was described as "grimacing, moaning, grunting, waking, and screaming." A propofol infusion was initiated at 30 mcg/kg/min (1.8 mg/kg/h), and allowed the reduction of opioid and benzodiazepine use (Fig. 2). The parents were noted to report that "he seemed comfortable, but that he occasionally grimaces or moans, which is controlled by the PCA boost."

TABLE 1. DEMOGRAPHICS OF THREE PEDIATRIC PATIENTS RECEIVING PALLIATIVE SEDATION THERAPY WITH PROPOFOL

	Patient 1	Patient 2	Patient 3
Age at diagnosis	9 years	6 years	11 years
Age at death	9 years	6 years	15 years
Sex	M	M	M
Weight (kg)	34.5	24.3	64
Initial oncology diagnosis	Angiosarcoma	Neuroblastoma	Acute lymphoblastic leukemia
Secondary diagnoses and complications	Lumbar and leg pain	HTN, PRES, GNS bacteremia, disseminated <i>Candida tropicalis</i> infection, severe abdominal pain	Acute disseminated encephalomyelitis, GVHD, MDR bacteremia, <i>Alcaligenes xylosoxidans</i> sepsis, possible Guillain-Barré syndrome, presumed pain

HTN, hypertension; PRES, posterior reversible encephalopathy syndrome; GNS, gram-negative *Staphylococcus*; GVHD, graft-versus-host disease, MDR: multiple drug resistant.

FIG. 1. Patient 1. Summary of infusions for pain control and sedation. Shown are opioid (Op) total dosages, with clinician boluses (CB), and boosts/attempts per 24-hour period [M, midazolam; ME, morphine equivalent; propofol dose calculation: $\text{mg/kg/hr} = 0.06 \text{ (mcg/kg/min)}$].

FIG. 2. Patient 2. Summary of infusions for pain control and sedation. Shown are opioid (Op) total dosages, with clinician boluses (CB), and boosts/attempts per 24-hour period [B, benzodiazepine; ME, morphine equivalent; propofol dose calculation: $\text{mg/kg/hr} = 0.06 \text{ (mcg/kg/min)}$].

FIG. 3. Patient 3. Summary of infusions for pain control and sedation. Shown are opioid (Op) total dosages, with clinician boluses (CB), and boosts/attempts per 24-hour period [M, midazolam; ME, morphine equivalent; propofol dose calculation: $\text{mg/kg/hr} \times 0.06 = (\text{mcg/kg/min})$].

The family chose to discontinue total parenteral nutrition and agreed to a DNAR order before the addition of propofol, and the child died on the day after the infusion started.

Case 3. A 15-year-old boy had acute lymphoblastic leukemia that had relapsed after bone marrow transplantation, accompanied by a secondary diagnosis of progressive leukoencephalopathy with complete neurologic devastation requiring ventilator support. He had been an inpatient for 10 months. During this time he was diagnosed with graft-versus-host disease, multiple-drug-resistant bacteremia, and possible Guillain-Barré syndrome. The patient was on ventilator support via tracheostomy and was receiving fentanyl and midazolam infusions with boost doses for sedation. After he developed *Alcaligenes xylosoxidans* septic shock, the mother agreed to a DNAR order and requested the withdrawal of antibiotics, which were ineffective in treating his life-threatening infection. During the 8 hours before initiation of propofol treatment, the patient required an increasing frequency of midazolam and fentanyl boosts for pain and suffering, as indicated by "grimacing and clenching teeth." These signs were distressing to the mother, who expressed concern about his level of comfort during the dying process; 3 days after the DNAR order, propofol was started at 60 mcg/kg/min (3.6 mg/kg/h). Over the following 2 days, the patient required no further increases in propofol, fentanyl, or midazolam (Fig. 3). The mother was noted to report that "he appears comfortable"; the patient died on day 3 of propofol infusion.

Pain scores and sedation status

Patients 1 and 2 continued to experience severe pain at all assessments while awake (Table 2); however, the introduction of propofol markedly increased the number of assessments recorded as asleep/sedated. Patient 3 received propofol in response to the mother's concern that he was still suffering and her desire for his improved comfort as he approached the end of life; all subsequent assessments reflected sedation.

Discussion

Ours is the first study to concurrently evaluate pain intensity, sedation status, and quality of palliative sedation in pediatric oncology patients receiving propofol PST at the end of life. Our experience shows that propofol PST is a useful palliative option for such patients.

Our review of pain measures and sedation status before and during propofol PST allowed us to evaluate the effectiveness of palliation. Clinicians continued to assess pain in these patients whenever possible (Table 2). The elevated pain scores before and after initiation of propofol in cases 1 and 2 reflected the need for sedation to relieve extreme suffering. In these cases, propofol PST provided effective palliation of agitation and anxiety, even when pain could not be adequately controlled. Although the sedation regimen in the third case appeared to be adequate on the basis of sedation assessments, the patient's mother perceived continued suffering and agitation, and propofol was added to ensure adequate palliation. We propose that pain scores did not improve (much like they

TABLE 2. PAIN SCORES AND SEDATION STATUS OF THREE PEDIATRIC PATIENTS RECEIVING PALLIATIVE SEDATION WITH PROPOFOL AT THE END OF LIFE

	Day -2	Day -1	Day 0 ^a	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
<i>Patient 1</i>											
Total number of attempted pain assessments	9	11	22	10	11	13	9	16	9	13	11
Number (%) of asleep/sedated pain assessments	2 (22.2%)	3 (27.3%)	15 (68.2%)	5 (50%)	7 (63.6%)	5 (38.5%)	5 (55.6%)	2 (12.5%)	8 (88.9%)	13 (100%)	11 (100%)
Number of evaluable pain assessments	7	8	7	5	4	8	4	14	1	0	0
Mean pain score	8.4	9.1	8.4	10	8.7	7.9	10	8	10	N/A	N/A
<i>Patient 2</i>											
Total number of attempted pain assessments	21	19	10	8	-	-	-	-	-	-	-
Number (%) of asleep/sedated pain assessments	3 (14%)	2 (10.5%)	9 (90%)	5 (62.5%)	-	-	-	-	-	-	-
Number of evaluable pain assessments	18	17	1	3	-	-	-	-	-	-	-
Mean pain score	7.4	8.6	10	4	-	-	-	-	-	-	-
<i>Patient 3</i>											
Total number of attempted pain assessments	23	5	5	6	6	2	-	-	-	-	-
Number (%) of asleep/sedated pain assessments	23 (100%)	5 (100%)	5 (100%)	6 (100%)	6 (100%)	2 (100%)	-	-	-	-	-
Number of evaluable pain assessments	0	0	0	0	0	0	-	-	-	-	-
Mean pain score	N/A	N/A	N/A	N/A	N/A	N/A	-	-	-	-	-

^aDay 0 = the first day of palliative sedation with propofol.

did not improve from maximized pain therapy), but that the increased frequency of assessments noted as "asleep" serves as a measure of the adequacy of the PST approach to relieve suffering.

To our knowledge, the use of propofol for PST in children has been described in only two case reports and a series of 9 patients. Tobias reported the addition of a propofol infusion to a hydromorphone infusion for 16 hours in a 14-year-old girl with disseminated T-cell lymphoma and unrelieved suffering.¹⁴ Glover et al. reported concurrent propofol and hydromorphone infusions for 10 days in a 3-year-old girl with advanced rhabdomyosarcoma.¹² In the largest report, Hooke and colleagues retrospectively described the use of propofol PST in nine terminally ill patients 1–18 years old; propofol was infused for a median of 5 days (range 1–30 days), and was continued to the time of death in eight patients.¹³ The three patients in our series received propofol infusions for 9 days, 35 hours, and 3 days, respectively, until the time of death. Propofol was briefly discontinued twice in one patient.

Hooke et al. reported one patient in their series who had undergone a celiac nerve block injection 1 month before propofol infusion.¹³ Our second patient had had an epidural catheter inserted 1 month before propofol PST to relieve localized abdominal pain. However, despite ongoing epidural analgesia (and possibly because of disease extension beyond the epidural analgesic coverage), this patient experienced intractable suffering ameliorated only by propofol sedation.

Propofol can cause severe adverse cardiorespiratory effects, especially when given in conjunction with opioids and benzodiazepines. However, these effects should be minimal when small doses are administered by highly trained staff,^{20–23} and the recommended dose regimens are applied. All 3 cases reported here received propofol infusions in the intensive care unit and were cared for by pediatric intensivists and/or pediatric pain specialists with training in anesthesia. The indications, advantages, and disadvantages of propofol PST are reviewed in Table 3; the dose regimens employed in our experience and the existing literature reflecting the use of propofol for PST are presented in Table 4. Some authors^{12,14} describe the use of bolus doses initially, while we and others initiated propofol therapy without a bolus. Tobias recommended starting with a 0.5-mg/kg bolus, followed by a continuous infusion of 0.5 mg/kg/h, escalating the dosage as needed.¹⁴ Titration of the infusion rate or additional boluses is recommended in order to provide comfort and relieve suffering.^{12,14} Our propofol infusion rate starting doses are at the higher end of the range of reported regimens of propofol PST (Table 4); nevertheless, respiratory depression was not noted in any of our cases. Patient 1, who had the longest duration of propofol infusion (9 days), experienced hypotension during the last 2 days of life, but no other propofol side effects were observed. All cases reported in this series required infusion rate increases and/or additional bolus doses to achieve and maintain the desired level of sedation. Because our primary goal was palliation, no laboratory studies were ordered.

We maintained our patients' opioid infusions after the initiation of propofol. Before propofol PST our patients required sharp, rapid escalation of their opioid dosages to relieve pain. Patient 1 initially received 13 mg/kg/h ME, which had increased to 23.2 mg/kg/h ME at the initiation of propofol PST, and to 49.3 mg/kg/h at the time of death. Patient 2 received 4.9 mg/kg/h ME initially, 20.6 mg/kg/h ME after

TABLE 3. INDICATIONS, ADVANTAGES, AND DISADVANTAGES OF THE USE OF PROPOFOL AS PALLIATIVE SEDATION THERAPY (PST)

Indications for propofol PST	Relief of suffering caused by intractable pain, anxiety, or agitation, refractory to standard palliative therapy (see Fig. 4).
Advantages/benefits of propofol PST	Rapid onset; easily titrated to effect; rapid recovery; good safety profile when administered by trained personnel; ²⁰⁻²³ possible down-titration of other sedating regimens
Disadvantages/risks of propofol PST	Requires trained personnel and controlled care setting; ²⁰⁻²³ potentially incompatible with other intravenous medications; respiratory depression and/or airway obstruction; ²³ hemodynamic instability (hypotension); ¹⁵ hypertriglyceridemia; ¹⁵ potential infectious risk of lipid solution; ¹⁵ propofol infusion syndrome (cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure) ^{15,34,35}

initiation of propofol PST, and 8.1 mg/kg/h ME at the time of death. Patient 3 received 0.08 mg/kg/h ME initially, and 1.25 mg/kg/h after the initiation of propofol PST; this infusion rate remained unchanged for 2 days prior to death. Tobias reported a hydromorphone continuous infusion of 170 mg/h (19 mg/kg/h ME),¹⁴ while Glover et al. reported an initial hydromorphone infusion of 10 mg/h (3.9 mg/kg/h ME), that was subsequently increased to 15 mg/h (5.85 mg/kg/h ME).¹² Hooke et al. reported a mean initial ME of 2.4 mg/kg/h, and a mean maximum ME of 7.8 mg/kg/h in their 9 patients; the highest opioid infusion dosage in the series was 46 mg/kg/h ME, and two patients required significant increases in opioid dosage after propofol was initiated (maximum dose of 14 to 81 times the initial dose).¹³

Recommendations for end-of-life PST decisions

The purpose of PST is to relieve symptoms that are refractory to traditionally used medications, and that cause great distress to the imminently dying patient.²⁴ The success of PST is measured by achievement of the therapeutic intent (patient comfort), and not by whether death is hastened or delayed; therefore euthanasia is not a consideration. Although the term "imminently dying" is not formally defined, the patient is expected to die naturally of the underlying disease and PST is assumed not to shorten life.²⁵ When appropriately used, PST is reported not to reduce the duration of survival in adults,²⁶⁻²⁸ although there are no comparable data for pediatric patients. In general, good pain and symptom control lead to longer survival.²⁷

Palliative sedation is an option for pediatric patients clinically considered to be (1) imminently dying, and (2) experiencing intolerable suffering not responsive to other modalities. If the prognosis is unclear, we recommend a staff team meeting to clarify it. If these two conditions are met, an interdisciplinary team should review the comfort interventions to ensure that

the symptoms are truly refractory rather than poorly controlled. Maximizing traditional interventions (titration of continuous opioid infusion, rotation or addition of opioids, or initiation and titration of benzodiazepine infusion) may relieve suffering that is not truly refractory, and a timed trial of such interventions, using measurable end-points, should decide the issue. If suffering is not adequately reduced within the established time limit, PST should be discussed as the "therapy of last resort."^{1,24} In our 3 cases, sedation with a first-line agent was attempted (midazolam and dexmedetomidine infusions, and/or intermittent lorazepam doses), and was considered to have failed before propofol was administered. Figure 4 provides an algorithm that may clarify these considerations. In our experience, propofol PST has only been used in cases in which sedation with other agents has failed to achieve relief of suffering at the end of life. A pain and/or palliative care team consultation is strongly recommended.²⁸

Patient and family wishes should be considered. Some patients prefer to tolerate a certain amount of pain in order to remain more alert, whereas others choose relief of pain, even if it requires increased sedation.²⁹ We recommend an interdisciplinary family care conference to increase the likelihood that children and families receive end-of-life care consistent with their wishes.³⁰ Such a conference allows the clarification of goals, evaluation of options, discussion of a time-limited trial of maximal traditional therapies, and discussion of the option of PST. Wolfe et al. identified a considerable delay in parents' recognition that their child has no realistic chance of cure; therefore it is important that these discussions include clear explanations of prognosis and of the goal of PST.³¹ The continued use of life-sustaining interventions (artificial nutrition and hydration, dialysis, and antibiotic usage) should be considered independently of PST, although we recommend discussion of these options and formulation of a care plan before initiation of PST.^{3,32} Artificial nutrition and hydration are not contraindicated in

TABLE 4. SUMMARY OF REPORTED PROPOFOL DOSES USED FOR PEDIATRIC PALLIATIVE SEDATION THERAPY

Source	n	Duration of infusion days (range)	Initial bolus dose (mg/kg)	Starting infusion dose mg/kg/h (range)	Maximum infusion dose mg/kg/h (range)
Current report	3	(2-9)	None	(1.8-3.6)	(3.6-7.8)
Glover et al., 1996 ¹²	1	10	1.2	1.2	7.2
Tobias et al., 1997 ¹⁴	1	1	0.43	0.43	0.86
Hooke, 2007 ¹³	9	(1-30)	None	(0.28-1.4)	(0.7-12.0)

FIG. 4. Algorithm for initiation of palliative sedation therapy (PST), including selection of propofol. A timed trial of optimized symptom-directed measures is suggested at appropriate times (IDT, interdisciplinary team; FCC, family care conference; POLST, physician orders for life-sustaining treatment; DNAR, do not attempt resuscitation; ANH, artificial nutrition/hydration).

patients receiving PST, but may reduce comfort by contributing to fluid overload or gastrointestinal distress.³² To ensure patient comfort at the end of life, we recommend that a DNAR form be signed and placed on the chart before initiation of PST.

Although children do not usually make their own care decisions, many children with a lengthy illness experience develop opinions about their care and should be allowed to express their feelings and care goals. Planning should incorporate age-appropriate discussions with the child. Whenever

possible, assent should be obtained from older children before initiation of PST.³³ It is the fiduciary responsibility of clinicians to act in the child's best interest regardless of family wishes; therefore requests for sedation should be evaluated objectively to ensure that they reflect patient distress rather than family distress about the child's poor prognosis.

The National Hospice and Palliative Care Organization recommends titration of sedation to the minimum reduction of consciousness necessary to tolerably control symptoms.³² Although patient preferences for deep versus lighter sedation may differ,³² deep sedation can offer either a temporary respite from intractable pain, or a means of controlling intolerable symptoms until natural death occurs. Patients and families must be advised of the small but real risk that sedating agents (propofol,^{34,35} high-dose opioids, and benzodiazepines) may hasten death, and some centers may consider using a written consent form. We recommend the use of objective symptom assessment measures to monitor patient comfort, response to therapy, and need to titrate sedation. Ongoing open communication and a mechanism to ensure that goals, plans, and family needs are periodically read-dressed are encouraged.^{3,30}

As PST is reserved for the small percentage of hospitalized dying patients with refractory symptoms, staff and family may be unfamiliar with this intervention. We recommend ongoing training of staff in high-quality palliative sedation care, and education of families and caregivers to ensure that they understand the solely palliative purpose of PST. Ethics consultation is recommended when there is disagreement about the prognosis, tolerability of symptoms, extent of suffering, or goals of care, and may be mandatory at some institutions.

Quality-improvement reviews should periodically examine: (1) indications for PST; (2) therapies tried before PST; (3) staff understanding of the goals of PST and support of family and patient; (4) the management of life-sustaining interventions during the PST process; (5) the process for titrating sedation; and (6) the occurrence and management of any complications.³² The review may include an analysis of the planning and implementation of sedation and the assessment of outcomes, including effectiveness and family satisfaction.³²

Conclusions

Our experiences and those previously reported indicate that propofol can provide significant palliation for the terminally ill child. Propofol PST allowed us to reduce the dose of opioids in one of our patients, while the others required minimal to no increase. Increasing the dose of propofol rather than of opioids can avert opioid side effects (nausea, vomiting, and constipation), while providing adequate palliation of refractory pain. The family members in all of our cases expressed concern about the comfort of their dying child, and reported that this concern was alleviated after propofol PST was introduced.

Propofol PST can be considered for any child with refractory suffering at the end of life, regardless of the underlying disease. Because PST should be an intervention of last resort, institutional policies and procedures can provide helpful guidance to physicians considering this option. Our algorithm provides a starting point for such guidance.

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Author Disclosure Statement

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