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Pain Management for Children during Bone Marrow and Stem Cell Transplantation

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Abstract

Pain management for children during bone marrow and stem cell transplantation is a significant clinical challenge for the health care team. Pain management strategies vary by institution. This paper reports on the use of a pediatric pain management service and patient-and caregiver-controlled analgesia for children undergoing transplant. This 2-year retrospective chart review examined the pain management practices and outcomes of children undergoing bone marrow and stem cell transplants in a large urban teaching hospital during 2008 and 2009. We concluded that patient- and caregiver-controlled analgesia is a well-tolerated modality for pain control during hospitalization for transplantation at this institution.

INTRODUCTION

Bone marrow and stem cell transplantation offers a potential cure for children with cancer and a spectrum of other diseases that are otherwise incurable (Krauss & Kamani, 2009; Myers & Davies, 2009; Prasad & Kurtzberg, 2010; Rocha et al., 2009). However, this treatment is not without multiple comorbidities, including the potential for significant nausea and vomiting, graft-versus-host disease, bacterial/viral/fungal infections, and gastrointestinal and pulmonary complications (Gassas, Sung, Doyle, Clarke, & Saunders, 2003; Messina et al., 2008; Staber, Langner, Dornbusch, & Neumeister, 2007; Styczynski & Gil, 2008; Vogelsang & Dala, 2002). Many of the complications after transplantation are associated with pain that requires careful consideration and treatment in this vulnerable population.

Gastrointestinal complications are often cited as a pain-provoking challenge for children in the posttransplant period. A retrospective study of 142 transplant procedures revealed that

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71% of children reported abdominal pain and 90% experienced painful mucositis (Barker, Anderson, Sauve, & Butzner, 2005). The most common gastrointestinal complication reported in the children after transplant is mucositis (Barker et al., 2005). Mucositis is the inflammatory and ulcerative process of the gastrointestinal tract resulting from an assault on the epithelial mucous membrane and is associated with administration of radiotherapy or chemotherapy. The incidence of painful mucositis has been reported to be as high as 90% in all transplant recipients, including both adults and children (Harris, 2006; Harris, Eilers, Harriman, Cashavelly, & Maxwell, 2008).

In addition to mucositis there are a multitude of other potential painful complications after bone marrow transplant. Neurotoxicity is an example of a posttransplant complication with the potential to produce pain ranging from neuralgia related to herpetic infections to neuropathy associated with immunosuppressive therapy, including calcineurin-inhibitor drugs (e.g., cyclosporine and tacrolimus) (Noda, Kodama, Yasuda, & Takahashi, 2008; Onozawa et al., 2009). Veno-occlusive disease is a painful complication resulting from damage to the sinusoid endothelial cells of the liver, leading to obstruction of intrahepatic vessels. In a recent study of 61 children (mean age 5.9 years) the incidence of veno-occlusive disease after transplant was 27%–40% and is associated with hepatomegaly, portal hypertension, and ascites (Miano, Faraci, Dini, & Bordigoni, 2008). Diarrhea and associated abdominal pain has been reported in as many as 67% of childhood transplant patients and may be caused by graft-versus-host disease, mucosal damage from chemotherapy, or infection (e.g., *Clostridium difficile*) (Barker et al., 2005).

Additionally, painful hemorrhagic cystitis occurs in up to 25% of children during hospitalization for transplantation and results from muscosal damage caused by chemotherapy or infection (Miano et al., 2008). BK virus, named from the initials of the first patient diagnosed with the infection in 1971, is a Papovavirus and is present in an asymptomatic state in 60%–100% of children (Shah, Daniel, & Warszawski, 1973). The BK virus is dormant in most hosts but may be reactivated during an immunocompromised state, which typically occurs after bone marrow transplant. The kidney is the most common site of reactivation, where the virus replication may lead to hemorrhagic cystitis (Reploeg, Storch, & Clifford, 2001).

Patient-controlled analgesia (PCA) is an effective treatment modality often employed during cancer treatment for management of acute pain. PCA delivery of opioids with or without ketamine has been shown to be effective in treating mucositis in the pediatric oncology population (White, Hommers, Parry, & Stoddart, 2011). PCA allows timely, individualized pain management for patients who are developmentally appropriate and cognitively intact (Nelson, Yaster, Kost-Byerly, & Monitto, 2010). Generally, children younger than 6 are in the preoperational stage of development and are unable to independently operate PCA, in which case surrogates such as parents or nurses may be better equipped to supervise this effective pain management strategy (Beilin & Fireman, 1999; Golianu, Krane, Galloway, & Yaster, 2000; Monitto et al., 2000). In a position statement published in 2007 the American Society for Pain Management Nursing (ASPMN) supported the use of authorized agent–controlled analgesia as “a method of pain control in which a consistently available and competent individual is authorized by a prescriber and properly educated to activate the

dosing button of an analgesia infusion pump when a patient is unable, in response to that patient's pain." The ASPMN goes on to recognize parents as appropriate agents for such caregiver-controlled analgesia (CCA) (Wuhrman et al., 2007). The use of family members and clinicians as proxy for PCA in pediatric oncology has been reported to be a safe alternative for younger patients and has an overall complication rate of 0.54% (Anghelescu et al., 2011). The purpose of this manuscript is to report on the practices of the pain management service and the use of PCA/CCA in the pediatric bone marrow and stem cell transplantation population at our institution.

PAIN MANAGEMENT PROCEDURE/STRATEGY

Effective pain control after transplantation requires constant attention and willingness on the part of the managing clinicians to evaluate and adapt pain-relieving strategies. One such method is a partnership between the primary oncology team (physicians, nurses, social workers) and a pediatric pain management team (PPMT) made up of attending anesthesiologists and pediatric nurse practitioners. The responsibilities of the PPMT range from routine dosage recommendations to full pain assessments and implementation/ monitoring of opioid and adjunct medications, including antipyretics, antiemetics, anxiolytics, neuropathic pain medications, peripherally acting agents, epidural formulas, and peripheral nerve catheter combinations. The PPMT also plays an active role in assisting to wean medications after prolonged use, which is often the case with the extended hospitalizations seen in this population.

Consults to the PPMT for bone marrow and stem cell transplant patients are initiated by the primary pediatric oncology service, the pediatric oncology nurses, or the children and their families. Roughly 90% of 40 annual oncology consults per year arise from nurses who understand the evolution of pain and have widespread familiarity with the benefits of early and integrated pain management. The PPMT begins by completing an extensive history to better understand the patient's previous pain experiences and to develop a comprehensive treatment plan. Subsequent to the initial consult, a PCA pump is almost always prescribed, with children 6 years of age and younger receiving a PCA by surrogate (caregiver-controlled analgesia). Depending on the severity of the pain, a continuous infusion may be used in conjunction with bolus dosing.

After transplantation, patients have complicated intravenous medication regimens, making compatibility an important consideration when choosing pain management medications. Because of its favorable compatibility profile, morphine is often the preferred opioid, with hydromorphone and fentanyl being feasible alternatives. Initial dosing of PCA opioids are listed in Table 1. An added clause to PCA orders permits nurses to adjust dosages up to 50% from initial dosing based on their bedside assessment and patient's pain scores. When a patient has reached his or her designated maximum, the PPMT is notified to adjust ranges or consider adjunct therapies.

Opioid receptors are present on three types of G proteins, G_s, $G_{i/o}$, and G_q. The analgesic effects of opioids are thought to result from the cascade of events ensuing from binding to the $G_{i/o}$ receptors, whereas binding to the G_s proteins is hypothesized to be responsible for

side effects, including pruritus, nausea, and vomiting (Crain & Shen, 2000). Naloxone has been shown to provide G_s receptor antagonism and in low doses to decrease excitatory side effects, including pruritus, nausea, and vomiting (Crain & Shen, 1996). For these reasons we use a concomitant naloxone infusion (1–2 mcg/kg/hr) to reduce the incidence and severity of opioid-induced side effects while maintaining the desirable analgesic effects (Maxwell et al., 2005). Table 2 lists the standard order set for drugs and doses used in conjunction with PCA to treat side effects not controlled with naloxone infusion. Common side effects may also be related to the transplant itself, and the oncology team assists with treating them as well. Not all pain in the posttransplant period is best treated with opioids, and Table 3 lists common adjunct medications and the types of pain they are used to treat.

Patient monitoring begins with initiation or increase in dose of PCA. This consists of hourly assessment for 4 hours and includes pain rating (age-appropriate scales), sedation level (0–5 Likert scale: 0 = nonresponsive; 1 = responds to pain only; 2 = drowsy but hard to arouse, needs tactile stimulus; 3 = drowsy but will open eyes when names is called several times; 4 = drowsy but easily aroused, opens eyes when name is called; 5 = awake, alert, and oriented times three), vital signs, and oxygen saturation (pulse oximetry is continuous for at least 24 hours). After the requirements for hourly assessments are completed, the interval is increased to every 4 hours and includes monitoring of pump settings and total basal/bolus doses. Monitoring for adverse effects, including those listed in Table 4, is completed every 4 hours. All assessments, including drug dosing, pain ratings, sedation levels, vitals, and reports of side effects, are recorded on the nursing pain flowsheet and reviewed daily by a member of the PPMT. Pain rating scales used for younger patients include Behavioral (nonverbal or cognitively impaired), Face, Legs, Activity, Cry, Consolability Scale (preverbal or nonverbal up to 7 years old) (Voepel-Lewis, Zanotti, Dammeyer, & Merkel, 2010), Faces (≥3 years old) (Tomlinson, von Baeyer, Stinson, & Sung, 2010) and Neonatal/Infant Pain Scale (0–9 months) (Hummel, Lawlor-Klean, & Weiss, 2010). Older, cognitively appropriate patients use a self-reported numerical rating scale.

Appropriate and safe weaning is a critical component of pain management after transplantation. Tolerance and withdrawal are commonly seen with prolonged opioid use and necessitate a thoughtful weaning process (Anand et al., 2010). PCA basal infusion is usually weaned by 10%–20% per day as dictated by the institutional PPMT protocols and as the patient tolerates and bolus dosing continues throughout the weaning process. Transition to enteral medications is mostly avoided because of slow gut recovery and the competition with multiple oral medications necessary as the patient begins to prepare for discharge. In the rare cases in which patients continue to have pain beyond discharge from the hospital or when dosing escalations employed during treatment requires conservative weaning beyond their length of stay, the patient is transitioned to enteral medications. In these cases it is necessary to continue weaning beyond hospitalization and follow-up in the outpatient setting is required.

METHODS

Institutional Review Board (IRB) approval and consent waiver for retrospective chart review were obtained. A list of 51 patients who underwent bone marrow and stem cell

transplantation at Johns Hopkins between December 2007 and January 2010 was generated from the transplant database. Data gathered by members of the research team included demographic data, underlying disease, conditioning regimen, type of transplant, etiology of pain, medication used for PCA, nursing-documented pain ratings before and after PCA, and any documented adverse reactions requiring intervention beyond medication prescribed on an as-needed basis. Cumulative opioid doses were calculated as morphine equivalents. Descriptive statistics, including median, interquartile range, and proportions, were calculated using Stata 10 statistical software (StataCorp., College Station, TX; Stata, 2007).

RESULTS

Sixty-nine percent (35/51) of the children in the 2-year period analyzed received PCA for management of transplant-related pain. Characteristics of the sample are described in Table 5. The mean age for those who were prescribed patient- or surrogate-controlled analgesia was 11.1 years (range 0.8–20). The mean day after transplant for beginning PCA was +3 (SD 5) after marrow/stem cell infusion. The cause of the pain at the time PCA was begun was mucositis in 97% (34/35) of patients; the remaining patient had headache associated with cyclophosphamide (Cytoxan) infusion.

Sixty-seven percent (8/12) of the children younger than age 6 who underwent transplantation were treated with PCA (caregiver controlled). The mean age of patients using PCA in the <6 years group was 35 months (SD 17) and mean weight was 14 kg (SD 2.5). Pain score before initiation of PCA for this group was 3/10 (SD 1.5) and in the 48- to 72-hour period after it fell to 0.7/10 (SD 0.6). The mean total milligrams-per-kilogram opioid dose for children younger than 6 years old was 21 mg/kg (SD 23) and mean days on PCA was 40 (SD 75). No significant adverse reactions were identified; in particular, no patients were documented to have respiratory depression or distress while receiving PCA.

The remaining 27 patients were >6 years of age. Pain score before initiation of PCA in this group was 4.9/10 (SD 2.5), and in the 48- to 72-hour period it fell to 1.9/10 (SD 1.6). The mean total milligrams-per-kilogram opioid dose for patients older than 6 years was 16 mg/kg (SD 14) and mean days on PCA was 25 (SD 28). No respiratory depression or distress or uncontrolled side effects were noted in this group. In addition, no patient in either group (</> age 6 years) discontinued PCA because of uncontrolled side effects.

Sixty-nine percent (11/16) of the children who did not receive PCA were transplanted with nonmyeloablative regimens, which consist of lower doses of chemotherapy. Of the five children who underwent a myeloablative regimen and no PCA, three received no opioid medications and the remaining two received morphine or oxycodone as needed only.

DISCUSSION

Bone marrow and stem cell transplantation is an intense therapy employed in the treatment of children with life-threatening diseases. Controlling pain during the transplantation period is an important quality-of-life issue and has the potential to affect recovery. This retrospective study confirms that mucositis was the most prevalent pain condition at the initiation of PCA in the posttransplant period. Adequate control of pain associated with

mucositis may lead to increased activity levels and facilitate oral ingestion of nutrition and medications, which are important steps necessary for recovery and discharge from the hospital.

Nurses are on the forefront of pain assessment and management in the pediatric oncology setting. The nurses in our facility play an important role in identifying patients who may benefit from PCA. The majority (35/51) of patients who received bone marrow and stem cell transplantation in the 2 years covered by this study used PCA for pain management, demonstrating the endorsement of this intervention by staff, patient, and families. Appropriate titrating of doses and timely administration of pain medication is a challenge for nurses caring for transplant patients. Parameters that allow the nurse to manipulate basal and bolus doses permit rapid response to changing medication needs.

It is not possible to appropriately identify or attribute all the possible side effects of PCA in our study because many of them overlap with toxicities from the transplant procedure itself. It should be noted though that none of the patients in our group discontinued PCA because of uncontrolled side effects or experienced any life-threatening adverse events. Procedures and protocols developed to guide this practice are essential to ensure safety, especially in younger patients who do not have the cognitive or motor developmental skills necessary to operate this technology. We have demonstrated with this study that, with the appropriate monitoring and education, caregiver-controlled analgesia can be a safe way to manage pain after bone marrow and stem cell transplantation in our population of child patients. Our experience contributes to the growing body of literature supporting the use of CCA in pediatric populations (Anghelescu, Burgoyne, Oakes, & Wallace, 2005; Czarnecki et al., 2011; Voepel-Lewis, Marinkovic, Kostrzewa, Tait, & Malviya, 2008).

Although the sample size does not allow for further analysis, the patients older than 6 years of age in this study remained on PCA longer than the older group (40 versus 25 days) and received a larger cumulative dose of opioids (21 mg/kg versus 15 mg/kg). Future research examining younger patients and PCA should focus on the use of surrogates for the assessment and management of pain and include models for identifying who is the most appropriate person to serve as surrogate and the best educational strategies for preparing surrogates for their role in controlling pain in this population.

FUTURE DIRECTIONS

Mucositis pain continues to be an important quality-of-life issue after bone marrow and stem cell transplantation. A recent Cochrane review identified 33 interventions for preventing mucositis in adult oncology patients, 12 of which have shown at least some evidence of benefit. Only four interventions have been shown effective in more than one trial and included amifostine, Chinese medicine, hydrolytic enzymes, and ice chips (Worthington, Clarkson, & Eden, 2007). Many of the prevention trials have included adults receiving radiation for head and neck cancer and may not be directly applicable for children undergoing bone marrow and stem cell transplantation. Although there are encouraging results using low-level laser for treatment of mucositis, opioid therapy remains the primary intervention for pain control (Clarkson et al., 2010). Oncology and pain management nurses

should take a lead in conducting research studies regarding patient and surrogate analgesia for the treatment of mucostitis and other acute pain conditions in pediatric populations, including those undergoing transplantation.

CONCLUSIONS

Bedside nurses play a critical role in assessing and controlling children's pain after bone marrow and stem cell transplants. Patient- and caregiver-controlled analgesia can be a safe and effective intervention for treating pain in children after bone marrow and stem cell transplantation. Multidisciplinary care, which includes oncology team members (both nurses and physicians) and pain management specialists, is reported to be an effective way to manage this intervention in our institution. A PPMT including specialized nurse practitioners is an important adjunct to safe and effective pain management in this complicated population of children undergoing bone marrow and stem cell transplants.

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Table 1

Initial Opioid Dosing for PCA

PCA Drug Used	Standard Basal Infusion Dosing	Standard Bolus Dosing
Morphine	20 mcg/kg/hr	20 mcg/kg/dose every 8 to 10 minutes as needed
Hydromorphone	4 mcg/kg/hr	4 mcg/kg/dose every 8 to 10 minutes as needed
Fentanyl	0.5 mcg/kg/hr	0.5 mcg/kg/dose every 8 to 10 minutes as needed

Table 2

Medications Used to Manage Side Effects

Potential Side Effect	Drug	Dose/Interval
Nausea/vomiting/pruritus	Diphenydramine	1 mg/kg q4h PRN
Nausea/vomiting	Ondansetron	1.1 mg/kg (max 4 mg) q4h PRN
	Promethazine	0.25–0.5 mg/kg q6h PRN
	Scopolamine topical patch	Place behind ear q3days
	Lorazepam	0.05–0.1 mg/kg q4h PRN
	Granisetron (Kytril)	1 mg q12h PRN
Muscle/bladder spasm	Diazepam	0.1 mg/kg q4h PRN
Constipation	Senokot	10 mg/kg daily

Table 3

Potential Adjunct Medications

General pain	Methadone	0.1 mg/kg/dose q6–12h
	Ketamine	10–25 mg PO
Neuropathic pain/chronic pain	Gabapentin	Start at 5 mg/kg/dose TID and increase to 15 mg/kg/dose TID
	Pregabalin	1 mg/kg/dose TID and increase to 3 mg/kg/dose TID
Tricyclic antidepressants	Amitriptyline	10/25/50 mg QHS
	Nortriptyline	10 mg QHS

Table 4

Potential Adverse Effects Monitored

Respiratory depression
Respiratory distress
Change in mental status (somnolence)
Nausea/vomiting
Urinary retention
Constipation
Pruritus

Table 5

Patient Characteristics

	PCA Group (n = 35)	Non-PCA Group (n = 16)
Age (years, mean, range)	11.1 (0.8–20)	12.5 (0.8–21.5)
Gender (males)	54% (19/35)	56% (9/16)
Weight (kg, mean, SD)	44 (27)	51 (29)
Diagnosis		
Solid tumor	37% (13/35)	44% (7/16)
Hematologic	49% (17/35)	19% (3/16)
Nonmalignant	14% (5/35)	38% (6/16)
Type of BMT		
Myeloablative	91% (32/35)	31% (5/16)
Nonmyeloablative	9% (3/35)	69% (11/16)
Prep regimen, including TBI	17% (6/35)	19% (3/16)

BMT = bone marrow transplant; PCA = patient-controlled anesthesia; TBI = total body irradiation.