Published in final edited form as:

Pain Manag Nurs. 2011 June ; 12(2): 82–94. doi:10.1016/j.pmn.2010.02.002.

Treatment of Pain in Children after Limb-Sparing Surgery: an Institution's 26-year Experience

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Abstract

A significant proportion of patients report long-term pain that is 5 or above on a 0 to 10 intensity scale after limb-sparing surgery for malignancies of the long bones. Patients experience several distinct types of pain after limb-sparing surgery, which constitute a complex clinical entity of pain post-limb sparing surgery. This retrospective study examined 26 years of experience in a pediatric institution (1981 through 2007) in pain management as far as 6 months after limb-sparing surgery and reviewed the historical evolution of pain interventions. One hundred and fifty patients underwent 151 limb-salvage surgeries for bone cancer of the extremities in this series. Pain treatment increased progressively in complexity. Therapies included opioids, nonsteroidal anti-inflammatory drugs, acetaminophen-opioid combinations, postoperative continuous epidural infusion, anticonvulsants and tricyclic antidepressants for neuropathic pain, local anesthetic wound catheters, and continuous peripheral nerve block catheters. Management of pain after limb-sparing surgery has evolved over the 26 years of this review. It presently relies on multiple "layers" of pharmacological and nonpharmacological strategies to address the complex mixed nociceptive and neuropathic mechanisms of pain in this patient population.

Keywords

limb sparing surgery; pain management; epidural; opioids; tricyclic antidepressants; anticonvulsants

Introduction

Current treatment for children and adolescents with malignant bone tumors involving the extremities combines chemotherapy with surgical removal of the tumor. The limb itself may be saved via limb sparing surgery (LSS), a procedure with safety, efficacy, and oncology outcome equivalent to those of amputation (Futani et al., 2006; Grimer, 2005; Nagarajan, Neglia, Clohisey, & Robison, 2002; Weisstein, Goldsby, & O'Donnell, 2005). Experience has revealed several distinct types of pain after LSS: 1) acute postoperative pain, 2) persistent long-term nociceptive pain associated with aggressive physical therapy, and 3) neuropathic pain (NP) related to intraoperative neural trauma. There is abundant information

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on the prevention and treatment of phantom limb pain after amputation (Bone, Critchley, & Buggy, 2002; Ehde et al., 2000; Fainsinger, de Gara, & Perez, 2000; Flor, 2002; Halbert, Crotty, & Cameron, 2002; Hall, Carroll, Parry, & McQuay, 2006; Hanley et al., 2007; Jahangiri, Jayatunga, Bradley, & Dark, 1994; Katz, 1997; McQuay, Moore, & Kalso, 1998; Nagarajan, Neglia, Clohisey, & Robison, 2002; Nikolajsen, Ilkjaer, Christensen, Kroner, & Jensen, 1997; Nikolajsen, Ilkjaer, Kroner, Christensen, & Jensen, 1997; Thompson, 1998); nevertheless, few reports have characterized pain post-limb sparing (PPLS). There is a need to describe this complex clinical entity and to develop principles for its management.

In a previous study of 65 patients, 82% of patients who had undergone LSS reported long-term PPLS; 33% reported a pain intensity of 5 or more on a scale from 0 to 10, and pain intensity was significantly correlated with interference with daily activities. The authors reported that persistent long-term pain may be caused by neuropathy (stretch injury to the peroneal nerve), fibrosis of soft tissues around the prosthesis, or weakness or instability of the joint; they recommended further review of the care of such patients to advance the design of effective pain management regimens that improve patients' ability to meet functional goals (Hudson et al., 1998).

The purpose of this study was to review the data pertaining to prolonged persistence of pain after LSS and to describe historical changes in pain management strategies for PPLS at St. Jude from 1981 through 2007.

Methods

Setting

St. Jude is a pediatric comprehensive cancer center. The age of patients at the time of diagnosis ranges from newborn to young adulthood. In 1990, the anesthesia service began offering pain consultations for management of PPLS; a formal, interdisciplinary pain management service was established in 2000, including anesthesiologists, clinical nurse specialists, psychologist, pharmacist, and physical therapist.

Patients

This retrospective review was approved by the St. Jude Institutional Review Board. The study population comprised individuals identified in the hospital database as having undergone LSS for cancer of the lower or upper extremity between January 1981 and August 2007. Patients whose tumors originated in soft tissue rather than bone were excluded.

Medical records review and data collection

A clinical research associate reviewed the medical records to identify each patient's demographic characteristics (age at diagnosis, sex, race), primary oncology diagnosis, tumor site, type of reconstructive surgery (autograft, allograft, metallic prosthesis, modular versus expandable prosthesis, etc.), postoperative complications, pain intensity scores, and details of postoperative pain management for up to 6 months.

Pain scores and the location and characteristics of pain were obtained from the charts and electronic records. The following specific pain management interventions were recorded: nonsteroidal anti-inflammatory drugs (NSAIDs); acetaminophen-opioid combinations; short-acting and long-acting oral opioids; transdermal or parenteral opioids, including intravenous opioid patient-controlled analgesia (PCA); epidural continuous analgesia; local anesthetic wound catheters at the surgical site; and continuous peripheral nerve block catheters. The following medications to treat NP were recorded: anticonvulsants

(gabapentin), tricyclic antidepressants (TCA, i.e., amitriptyline), and methadone. Pain assessment and pain intervention data were collected for each day of the first postoperative week, each week of the rest of the first month, and then each month for 6 months or until pain management follow-up ended.

Results

One hundred and fifty patients underwent 151 LSS for malignant bone tumors during the study period (1981 – 2007); one patient underwent an upper and a lower limb sparing surgery. Table 1 describes age at diagnosis, race, sex, primary diagnosis, and tumor site. The median age at diagnosis was 14 years (range, 6–21 years). Osteosarcoma was the most common diagnosis, and the distal femur was the most common tumor site. The mean annual number of LSS increased progressively over the study period, starting at 1.5 during the first decade (1981 to 1990), increasing to 6.8 during the second decade (1991 to 2000), and rising to 14.0 during the most recent period (January 2001 through August 2007). Table 2 lists the affected extremity and the prosthetic devices used. The lower extremity was most often affected; a modular metallic prosthesis was the most common device. Table 3 lists the timing and types of postoperative surgical complications; infection was the most frequent early complication, and wound revision was the most common delayed complication. Forty-two patients of 151 (27.8%) experienced 81 complications; twenty-two patients had more than one complication, six of which had both early and delayed complications. Table 4 summarizes the pain intensity scores according to length of pain management follow-up. In our series, pain intensity was better documented in the setting of acute postoperative pain (62.3% during days 0 to 7), particularly during days 0 to 3 (69.2% during days 0 to 3). Pain intensity was less documented during outpatient visits during weeks 2 to 4 (48.6%) and during the second month post-surgery (47%).

Pain intervention strategies evolved during the study period from unimodal analgesia to multimodal analgesia and interdisciplinary interventions, as illustrated in Figure 1. The specific pain management pharmacological interventions used are summarized in Table 5.

Discussion

Orthopedic surgery is among the most painful of surgeries (Lamontagne, Hepworth, & Salisbury, 2001) due to the significant muscular and skeletal tissue damage and reconstruction that are required and which cause both nociceptive and neuropathic pain (Marchettini, Formaglio, & Lacerenza, 2001). Specific postoperative pain syndromes after orthopedic surgery have been described, and the efficacy of a variety of multimodal analgesic techniques have been examined (Chiaretti & Langer, 2005; Kost-Byerly, 2002; Pasero & McCaffery, 2007; Sumpelmann & Munte, 2003; Verghese & Hannallah, 2005).

This study is the largest single institution review of the experience with PPLS over the 6 months period after LSS, covering a span of 26 years. Many changes in the management of pain can be observed over the time period that this review covers. One of the most significant changes is the increased attention to documentation and treatment of pain in children from 1981 to 2007. We believe that the finding of limited documentation of pain intensity is a reflection of both the historical under-appreciation of pain in children in the 1980's and 1990's, and the lack of a structured institutional pain service until 2000 to lead the implementation of cultural changes. Nevertheless, in our institutional experience, over time, there is a trend toward better assessment and documentation of pain intensity scores. In a series reporting on pain assessment and documentation at our institution, we found the rate of documentation of pain intensity scores had increased between 2000 and 2006 from 77% to over 95%. Compliance with documentation of the location and quality of pain was 97%

(range 92%–100%) and 91.3% (range 82%–96%) (Oakes, Angelescu, Windsor, & Barnhill, 2008). Due to the limited data regarding pain intensity, we are unable to comment on associations of pain severity with the types of surgical procedure or with the specific pain management interventions applied.

Optimal pain management after LSS at St. Jude addresses not only acute postoperative nociceptive pain, but also persistent long-term nociceptive pain related to prolonged physical rehabilitation, and NP related to surgery or chemotherapy. Pain caused by mechanical trauma and stretching of nerves during surgery may persist for weeks to months, independently of ongoing tissue injury or inflammation. The postoperative period often coincides with an intensive physical rehabilitation program (continuous passive movement, strengthening and stretching, assisted ambulation) that requires ongoing pain interventions. At St. Jude, physical rehabilitation may require as long as 6 months, even in the absence of postoperative complications or re-interventions. Physical therapy sessions are held daily during the inpatient postoperative period, and 3 to 5 sessions per week are required after discharge. Optimal postoperative pain relief both at rest and with movement have recently been emphasized to facilitate rehabilitation and timely discharge from the hospital (Joshi & Ogunnaik, 2005). Multimodal therapies that include two or more medications with different but complementary mechanisms, as well as nonpharmacological methods, are often used to achieve effective analgesia while reducing the required dose of each medication (Rosenquist & Rosenberg, 2003; White, 2005). Our institutional experience also reflects the concept of multimodal pharmacological and nonpharmacological therapies.

Historical changes in pain management strategies at St. Jude (1981 to 2007)

Over the years, clinicians at St. Jude have come to understand that PPLS represents a complex pain syndrome of mixed nociceptive and neuropathic pain. As new analgesic strategies were incorporated, stages in the evolution of pain management during the 26-year study period were defined, as indicated by the timeline represented in Figure 1.

The unimodal approach to nociceptive pain (1981)

Opioids remain the most important class of medications for relief of moderate to severe postoperative pain (Chiaretti & Langer, 2005; Pasero & McCaffery, 2007). In our review, oral short acting and long acting opioids were used in 60.3% and 48.3% of patients respectively, while intravenous opioids were used via PCA or non-PCA in 58.9% and 93.4% of patients respectively. Importantly, optimal opioid dosing is based on the temporal characteristics of pain. For intermittent episodic pain, patients use as-needed or around-the-clock doses of oral immediate-release opioids or intravenous (IV) opioids, whereas for continuous pain, continuous IV infusions, PCA, or oral long-acting opioids, plus additional breakthrough doses, are recommended (Chiaretti & Langer, 2005; Pasero & McCaffery, 2007; Rosenquist & Rosenberg, 2003). Short-acting opioids are used for immediate management of breakthrough pain and even NP episodes (in the context of an anticonvulsant and/or TCA regimen) (Eisenberg, McNicol, & Carr, 2005). Children 5 years or older who are expected to experience moderate to severe pain for at least 24 hours can benefit from PCA analgesia; it can also be safely used for younger children with the assistance of nurses or family members educated on the use of PCA (Angelescu, Burgoyne, Oakes, & Wallace, 2005; Chiaretti & Langer, 2005; Kost-Byerly, 2002; Wuhrman et al., 2007). PCA pumps were initiated at St. Jude in 1989.

Among opioids, morphine has been the gold standard for control of postoperative and chronic pain (Angelescu, Oakes, & Popenhagen, 2006; Chou, Clark, & Helfand, 2003; Collins & Weisman, 2003; Quigley, 2005; Vascello & McQuillan, 2006; Zernikow et al., 2006). In patients with cancer, chemotherapy-induced renal failure may cause accumulation

of the morphine metabolite morphine-6-glucuronide; therefore, hydromorphone or fentanyl may be preferable. Persistent, continuous pain is best managed with long-acting opioids. No specific long-acting opioid has been conclusively shown to be superior for treating chronic pain (Chou, Clark, & Helfand, 2003). The long-acting opioids used at St. Jude include oral preparations of morphine or oxycodone and transdermal fentanyl.

Addition of epidural analgesia (a bimodal approach) (1990)

In our series, 81.9% of patients with lower extremity LSS received epidural analgesia (118 of 144). The agents used in the epidural space include an opioid and/or a local anesthetic, which can provide excellent analgesia with less systemic sedation (Desparmet, Hardart, & Yaster, 2003). Historically at St. Jude, either an opioid only (fentanyl) or combinations of opioid and local anesthetic have been used. Currently, postoperative epidural analgesia uses bupivacaine 0.1% to 0.125% and fentanyl 3 to 5 mcg/ml for 3 to 5 days. The maximum acceptable bupivacaine infusion rate is 0.4 mg/kg/hr for older children and adults and 0.2 mg/kg/hr for infants (Verghese & Hannallah, 2005; Yaster, Tobin, & Kost-Byerly, 2003). Fentanyl doses should not exceed 0.5 to 1 mcg/kg/hr in order to minimize the risk of pruritus (Desparmet, Hardart, & Yaster, 2003), respiratory depression, and sedation.

Epidural analgesia is effective and safe in surgical cancer patients (de Leon-Casasola, Parker, Lema, Harrison, & Massey, 1994). During the 1990s, epidural analgesia became largely acceptable for use in children after orthopedic surgery of the lower extremities (Bruera & Kim, 2003; Caraceni et al., 2004; Desparmet, Hardart, & Yaster, 2003; Giaufre, Dalens, & Gombert, 1996; Goodarzi, 1999; Krane, Jacobson, Lynn, Parrot, & Tyler, 1987; Lovstad, Halvorsen, Raeder, & Steen, 1997). Epidural opioid analgesia targets drug delivery to the site of pain, thus requiring a lower dose of opioid, and exerts a synergistic effect with local anesthetics. In 1990, clinicians at St. Jude prepared to implement epidural analgesia by developing policies, procedures, and training for medical and nursing staff. As compared to intermittent IV doses, epidural analgesia can provide greater overall comfort with lower pain scores, less muscle spasm, and greater tolerance of physical activity during the initial postoperative period. Clinically significant central nervous system or respiratory depression attributed to epidural analgesia can be avoided by slow titration, careful monitoring of sedation levels and respiratory status, and reduction of the opioid dose when sedation increases. While patients receiving epidural analgesia post-LSS were initially managed in the ICU, they are now safely managed in non-ICU areas with frequent nurse observation and centralized pulse oximeter monitoring. In our experience, the concurrent use of IV opioids and epidural opioids does not increase the risk of respiratory or central nervous system complications (Anghelescu, Ross, Oakes, & Burgoyne, 2008).

Institutional efforts to improve pain management (1996)

Concomitant with an increased number of LSS at St. Jude, a Pain Committee was formed in 1996, which included the following disciplines: nursing, oncology, surgery, anesthesiology, neurology, psychology, and child life; a pain management service was established in 2000. This group of experts influenced the evolution of pain management for all St. Jude patients through policies, procedures, and standards of care. A multidisciplinary team approach is reported to be essential in providing optimal postoperative pain management by consistently evaluating pain syndromes and formulating plans for comprehensive continuing care (Berde & Solodiuk, 2003; Chiaretti & Langer, 2005; Kost-Byerly, 2002). Of particular note is the evaluation of pain intensity by using standardized age-appropriate pain assessment scales and the description of the characteristics of pain. As we have reported previously, in our institutional experience, we identified a trend to improve assessment and documentation of the characteristics of pain, as well as intensity and location of pain (Oakes, Anghelescu, Windsor, & Barnhill, 2008).

Development of a clinical algorithm for neuropathic pain (1997)

Surgical interventions for cancer can generate NP (Marchettini, Formaglio, & Lacerenza, 2001; Milch, 2005); its incidence and prevalence in children and adolescents are unknown (Berde, Lebel, & Olsson, 2003). Such syndromes respond incompletely to opioids (Fields, 1988; Portenoy, Foley, & Inturrisi, 1990; Rowbotham et al., 2003). Therefore, treatment includes anticonvulsants (Bone, Critchley, & Buggy, 2002) and TCAs (Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002; Rogers, 1989), which are known to have clinical efficacy. However, it is difficult to achieve complete pain control, and consensus about treatment options and dose titration is lacking (Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002). Although NP is not uncommon in cancer patients, only a small number of clinical research trials have specifically assessed analgesic drugs for cancer patients with NP (Caraceni et al., 2004; Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002). At St. Jude, we use an algorithm for NP in which anticonvulsants, TCA, and methadone are added sequentially if the response to the maximum dose of the previous drug is inadequate. Non-pharmacological interventions are also initiated before LSS and are continued long-term (Angelescu, Oakes, & Popenhagen, 2006; Berde, Lebel, & Olsson, 2003). Pharmacological therapies should be supplemented by multidisciplinary approaches such as physical therapy and psychological interventions. Since 1999, psychological interventions (guided imagery, distraction, self hypnosis) have been introduced by a clinical psychologist during one session 5 to 10 days before LSS; patients and family members were then encouraged to practice on their own the specific interventions as taught by the psychologist.

Assessment scales specific for NP have been described (Bennett, 2001; Galer & Jensen, 1997), but the traditional Faces Pain Scale (FPS) and Numerical Rating Scale (NRS) meet the requirements of validity and reliability and are extensively used in pediatric pain management. The Faces Pain Scale Revised has evidence for reliability and validity for pain assessment in children (Hicks, von Baeyer, Spafford, van Korlaar, & Goodenough, 2001). Clinical studies of NP should evaluate not only pain scores but also the descriptors of pain that are highly correlated with neuropathic pain conditions: electric shock, burning, cold, pricking, tingling, and itching (Bennett, 2001).

Since anecdotally NP is often persistent and is reported by our patients to interfere with sleep and rehabilitation after LSS, the pain management service evaluated the prevention and treatment of NP. Early recognition and aggressive therapy is thought to improve the prognosis (Dworkin et al., 2003; Halbert, Crotty, & Cameron, 2002). Opioid treatment of NP is often discouraged because of concerns about ineffectiveness, the development of tolerance, the risk of addiction, and limiting side effects (Eisenberg, McNicol, & Carr, 2005; Foley, 2003; Gallagher, 2006; Jacob, 2004). While NP has traditionally been considered less responsive to opioid therapy (Caraceni et al., 2004; Gilron, Watson, Cahill, & Moulin, 2006), controlled clinical trials and clinical experience suggest that a subpopulation of patients with NP may benefit from treatment with opioid analgesics (Benedetti et al., 1998; Eisenberg, McNicol, & Carr, 2005; Rowbotham et al., 2003).

Tricyclic antidepressants have demonstrated analgesic efficacy for NP entities such as post-herpetic neuralgia and diabetic neuropathy, and their use is extrapolated to other NP entities (Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002); they were found to be useful for phantom limb pain in children as early as 1989 (Rogers, 1989), taking effect within 1 week at doses lower than those required for depression (Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002). Amitriptyline is the TCA most commonly used in cancer patients with NP (Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002). The common starting dose for adults is 25 mg orally at bedtime (Dworkin et al., 2003; Mercadante, Arcuri, Tirelli, Villari, & Casuccio, 2002). In our series, amitriptyline was used in 12.6 % of patients. The St Jude Pharmacological Guidelines for Pain Management indicate a starting dose of 0.1 mg/kg

orally at bedtime, with the option of doubling the dose every 3 to 5 days up to a maximum dose of 1 mg/kg.

The anticonvulsant gabapentin emerged in 1993 and proved useful for the treatment of NP in adults and children (McClain & Ennevor, 2000), including postherpetic neuralgia, diabetic neuropathy (Bone, Critchley, & Buggy, 2002; Dahl, Mathiesen, & Moiniche, 2004; Gilron et al., 2005) and post-mastectomy pain (Dirks et al., 2002; Fassoulaki, Triga, Melemini, & Sarantopoulos, 2005). Gabapentin's low side effect profile and lack of drug-drug interactions made it preferable to the TCAs. Because it does not appear to significantly affect hematopoiesis, gabapentin may be the drug of choice for children with cancer and NP. It has been used successfully in the treatment of phantom limb pain in adults (Bone, Critchley, & Buggy, 2002), children and adolescents (Bone, Critchley, & Buggy, 2002; Rusy, Troshynski, & Weisman, 2001) and for cancer-related NP in adults (Caraceni et al., 2004) and children (Jacob, 2004). Gabapentin has been in use for NP at St. Jude since 1997. In this series, gabapentin has been used in 50.3% of patients. The St. Jude pain management guidelines recommend an initial dose of 5 mg/kg/day given in three divided doses every 8 hours and dose escalation every 2 to 3 days to a maximum of 70 mg/kg/day, not to exceed 3600 mg/day (Dworkin et al., 2003; Fassoulaki, Triga, Melemini, & Sarantopoulos, 2005; Krane, Golianu, & Leong, 2003; McClain & Ennevor, 2000). The onset of analgesia occurs as early as the third day for most patients (McClain & Ennevor, 2000).

Over the years, practice at St. Jude has changed so that TCAs are prescribed for NP as a second-line therapy after the maximum dose of gabapentin has been tried. The side effects of both medications are minimized by starting at a low dosage and increasing the dose every 3 to 5 days until pain relief is achieved or the maximum dose is reached. Because neuropathic pain is not always satisfactorily treated with gabapentin and TCA, the efficacy of other anticonvulsants such as pregabalin, topiramate, and lamotrigine is under investigation in adults with neuropathic pain and/or postoperative pain (Dahl, Mathiesen, & Moiniche, 2004).

Preemptive use of gabapentin (2000)

In our institutional experience, the pain management service and surgical team meet with the patient and family pre-operatively to discuss options for postoperative analgesia and epidural analgesia. Gabapentin is started 1 to 3 days preoperatively to allow plasma drug level to rise before surgical trauma to the nerves, at a dose of 5 mg/kg/day divided into three doses every 8 hours; after surgery the dose is increased every 2 to 3 days as indicated for neuropathic symptom control.

Post-operative pain is a type of nociceptive pain; however, it also comprises inflammatory, neurogenic, and visceral mechanisms, leading experts to consider it a transient type of neuropathic pain (Dahl, Mathiesen, & Moiniche, 2004; Milch, 2005). Therefore, preoperative use of gabapentin may have a place in the treatment of postoperative pain (Dahl, Mathiesen, & Moiniche, 2004; Ho, Gan, & Habib, 2006; Milch, 2005) and has been given as a single dose (Dirks et al., 2002; Hurley, Cohen, Williams, Rowlingson, & Wu, 2006; Rorarius et al., 2004) or as an adjunct to epidural analgesia (Turan, Kaya, Karamanlioglu, Pamukcu, & Apfel, 2006). Reports of the success of preemptive gabapentin treatment have been mixed (Adam, Menigaux, Sessler, & Chauvin, 2006; Dahl, Mathiesen, & Moiniche, 2004), and further studies are warranted.

Current Directions at St. Jude

Local anesthetic wound catheters (LAWC)

In this series bupivacaine 0.25–0.5% (2.5–5 mg/ml) (maximum dose 0.4 mg/kg/hr) via LAWC was used for 24–36 hours postoperatively to reduce pain conduction from the peripheral nerves to the spinal cord and to reduce the required dosage and side effects of systemic analgesics. The catheters are placed in the surgical field intraoperatively and local anesthetic is infused via a spring-loaded syringe or pump (White, 2005).

Continuous peripheral nerve block

(CPNB) infusions have largely replaced LAWC at St. Jude since 2005, as the literature indicates CPNB to be effective in adults (Capdevila et al., 2005) and children (Dadure et al., 2003), with a low incidence of major neurological and infectious adverse events (Capdevila et al., 2005). In a comparison knee surgery study, femoral CPNB resulted in lower pain scores and less use of opioids and NSAIDs than did LAWC, at rest and with movement (Dauri et al., 2009). Clinical trials of CPNB revealed better analgesia, consistently lower opioid requirement, less frequent postoperative nausea and vomiting, higher patient satisfaction, rarer complications, and a shorter duration of hospitalization in comparison to systemic opioids (Liu, Richman, Thirlby, & Wu, 2006; Siddiqui, Cepeda, Denman, Schumann, & Carr, 2007).

In a study comparing the effectiveness and safety of CPNB and patient-controlled epidural analgesia (PCEA) to that of opioid IV PCA, both CPNB and PCEA yielded lower mean dynamic and resting pain scores (Popping et al., 2008). Another study found CPNB and epidural analgesia to be superior to IV PCA in pain control, analgesic requirement, and patient satisfaction; no difference was detected in functional outcome. In addition, pruritus occurred less frequently in the CPNB group (Raimer et al., 2007).

Methadone

In this series, methadone was used in 4% of patients. Methadone for pain management in adults is well described (Nicholson, 2004; Nicholson 2007); nevertheless, pediatric studies are limited compared to adult studies. Methadone has been used in children for various pain entities, including acute procedure-related pain for burn care (Williams, Sarginson & Ratcliffe, 1998), other types of non-cancer pain in hospitalized children (Shir, Shenkman, Shavelson, Davidson, & Rosen, 1998), and for severe cancer-related pain (Sabatowski, Kasper, & Radbruch, 2002), chronic cancer-related pain (Martinson et al., 1982; Rowbotham et al., 2003), and cancer-related end of life care (Sirkia, Hovi, Pouttu, & Saarinen-Pihkala, 1998). In adults, methadone is also used for neuropathic pain entities: phantom limb pain (Bergmans, Snijdelaar, Katz, & Crul, 2002), diabetic neuropathy (Hays, Reid, Doran, & Geary, 2005), intractable neuropathic non-cancer pain (Altier, Dion, Boulanger, & Choiniere, 2005; Moulin, Palma, Watling, & Schulz, 2005), neuropathic pain related to burns (Altier, Dion, Boulanger, & Choiniere, 2001), and cancer-related neuropathic pain (Makin & Ellershaw, 1998).

Methadone's combined action as a mu opioid agonist and an N-methyl-D-aspartate receptor antagonist may render it uniquely effective for some patients with neuropathic pain that does not respond to TCA and gabapentin (Bergmans, Snijdelaar, Katz, & Crul, 2002; Foley, 2003; Lynch, 2005; Moulin, Palma, Watling, & Schulz, 2005). Advantages include its lack of known metabolites, excellent absorption after oral administration, and low cost. However, its long and unpredictable half-life requires careful titration to avoid overdose; more research in the area of safe administration is needed (Moulin, Palma, Watling, & Schulz, 2005). Significant side effects can be avoided with low doses (2–5 mg b.i.d. or t.i.d.) and

slow titration upward until satisfactory pain relief is achieved or intolerable side effects are noted (Bergmans, Snijdelaar, Katz, & Crul, 2002).

Epidural clonidine

In our series, we used the addition of clonidine to local anesthetics and opioids in epidural infusion in 5.6% of patients with lower extremity LSS. In pediatric studies, epidural clonidine added to local anesthetics prolongs the duration of epidural (caudal) analgesia (Yildiz, Korkmaz, Solak, & Toker, 2006), and continuous epidural infusions of local anesthetic and clonidine provide similar postoperative analgesia with fewer side effects (vomiting and pruritus) than local anesthetic and opioid combinations. Studies in adults and children have demonstrated the analgesic efficacy and safety of epidural clonidine in the management of acute postoperative pain, including pain after orthopedic surgery (Farrar & Lerman, 2002).

Limitations

Pain assessment tools and documentation methods changed during the 26-year study period at St. Jude; these changes are not examined in this review. The limited data regarding pain scores reflects the historical lack of awareness about pain in children and its treatment. Furthermore, neuropathic pain scales were not used to measure the presence or intensity of neuropathic pain. Although neuropathic pain can be difficult to distinguish from other types of chronic pain, neuropathic pain assessment scores contribute to diagnostic certainty (Bennett et al., 2007; Bennett, Smith, Torrance, & Lee, 2006). Even though this study was designed to review pain management after LSS for as long as 6 months, it cannot be determined with certainty that persistent long-term pain was mainly neuropathic in nature. This question is being addressed by a current prospective study at St. Jude. Nonpharmacological approaches are a part of our current standard of care but were not used or documented consistently over the 26 years reviewed.

Conclusions

Implications for nursing care to provide optimal pain management for children undergoing LSS emerge from the concept of a rational multimodal approach to include pharmacological, behavioral, and rehabilitation principles. Regimens to alleviate neuropathic cancer pain (Caraceni et al., 2004) and phantom limb pain (Bone, Critchley, & Buggy, 2002), incorporating gabapentin, opioids, TCA, and/or methadone, may be necessary to provide effective analgesia after LSS. Optimal pain control can improve postoperative outcomes, particularly in combination with a rehabilitation program that emphasizes early mobilization and early return to normal activities (Joshi & Ogunnaike, 2005). When acute pain is not well managed, the patient is at greater risk of chronic persistent pain (Joshi & Ogunnaike, 2005).

Multimodal pain therapy is effective (Chiaretti & Langer, 2005), and a multimodal approach that incorporates newer therapies is generally accepted in clinical practice. However, there is no consensus about the optimal combination regimen, and a systematic comparison of regimens is needed. Because regimens that combine pharmacologic and nonpharmacologic treatments have received even less attention in patients with persistent pain, it is unclear whether the addition of physical and/or psychological therapy provides additional benefit.

It is important for nurses to be aware of rescue analgesia strategies, such as PCA analgesia to protect against breakthrough pain on ambulation, end-of-dose failure on controlled-release opioids, or spontaneous pain with no obvious pathology (Chiaretti & Langer, 2005). Clinical experience in the use of multimodal therapy may allow the development of protocols for pain management through an interdisciplinary approach that incorporates input

from diverse members of the clinical care team (nursing, surgery, anesthesia, psychology, physical therapy, pharmacy).

Acknowledgments

We thank Sharon Naron and Lane Faughnan for editorial advice.

This work was supported in part by NIH Cancer Center Support Core Grant CA-21765 and by the American Lebanese Syrian Associated Charities (ALSAC).

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Figure 1. Evolution of Pain Management for Limb Sparing Surgery (1981 to 2007)

Abbreviations: NSAIDs: Nonsteroidal anti-inflammatory drugs; PCA: Patient-controlled analgesia; TCAs: Tricyclic antidepressants; LAWC: Local anesthetic wound catheter; PCEA: Patient controlled epidural analgesia; CPNB: Continuous peripheral nerve block.

Table 1
Patient Characteristics (n=151)

Characteristic	n (%)
<i>Age (yrs)</i>	
<10	20 (13.3)
≥10 to <18	109 (72.1)
≥18	22 (14.6)
<i>Race</i>	
White	108 (71.5)
Black	32 (21.2)
Other	11 (7.3)
<i>Sex</i>	
Female	74 (49)
Male	77 (51)
<i>Primary Diagnosis</i>	
Osteosarcoma	130 (86.1)
Ewing's sarcoma	14 (9.3)
Other	7 (4.6)
<i>Tumor Location</i>	
Distal femur	84 (55.6)
Proximal tibia	30 (19.9)
Proximal femur	13 (8.6)
Proximal fibula	7 (4.6)
Proximal humerus	5 (3.3)
Mid femur	4 (2.7)
Other lower	2 (1.3)
Mid tibia	1 (0.66)
Distal humerus	1 (0.66)
Distal ulna	1 (0.66)
Other upper	1 (0.66)
Distal tibia	1 (0.66)
Distal fibula	1 (0.66)
Rib	1 (0.66)

Table 2
Limb Sparing Surgery Site and Device Used

Surgery Type	Total n=151	Upper Extremity n=9	Lower Extremity n=142
Allograft	11	2	9
Autograft	2	0	2
Metallic Prosthesis			
<i>modular</i>	62	1	61
<i>expandable</i>	15	1	14
<i>combination modular/expandable</i>	8	0	8
<i>combination modular/allograft</i>	5	2	3
<i>combination metallic/autograft</i>	0	0	0
<i>combination custom/allograft</i>	1	0	1
Other			
<i>custom</i>	27	3	24
<i>miscellaneous^I</i>	9	0	9
<i>no prosthesis</i>	6	0	6
<i>missing data</i>	5	0	5

^I Miscellaneous = IM nail, Austin-Moore, fixed prosthesis.

Table 3
Post-operative Surgical Complications

	N=151 (Patient)	n=42 (Complication)
No information	18 (11.9%)	NA¹
No	91 (60.3%)	NA¹
Yes	42 (27.8%)	81
<i>Early (within 1 month)</i>	10 (6.6%)	14
<i>Type</i>		
Infection	6	7
Wound dehiscence	2	2
Thrombosis	1	1
Wound revision	2	2
Other ²	2	2
<i>Delayed (within 2–6 mos)</i>	38 (25.1%)	67
<i>Type</i>		
Wound revision	20	25
Infection	18	20
Wound dehiscence	8	8
Other ²	5	7
Dehiscence with infection	5	5
Broken prosthesis	1	1
Thrombosis	1	1

¹ NA: not applicable.

² Other: e.g. cellulitis with negative cultures, burns on toes, stress fracture, pulled muscle, necrosis of toes distal to surgical site.

Table 4

Distribution of Pain Scores (n=151)

Time Point	0 to 3 n (%)	4 to 6 n (%)	7 to 10 n (%)	Not documented n (%)
Day 0	24 (15.9)	31 (20.5)	44 (29.1)	52 (34.4)
Day 1	33 (21.9)	34 (22.5)	44 (29.1)	40 (26.5)
Day 2	41 (27.2)	29 (19.2)	34 (22.5)	47 (31.1)
Day 3	46 (30.5)	29 (19.2)	29 (19.2)	47 (31.1)
Day 4	39 (25.8)	34 (22.5)	33 (21.9)	45 (29.8)
Day 5	38 (25.2)	30 (19.9)	22 (14.6)	61 (40.4)
Day 6	40 (26.5)	25 (16.6)	7 (4.6)	79 (52.3)
Day 7	42 (27.8)	14 (9.3)	10 (6.6)	85 (56.3)
Week 2	50 (33.1)	20 (13.3)	16 (10.6)	65 (43)
Week 3	45 (29.8)	11 (7.3)	12 (8)	83 (55)
Week 4	46 (30.5)	10 (6.6)	10 (6.6)	85 (56.3)
Month 2	47 (31.1)	13 (8.6)	11 (7.3)	80 (53)
Month 3	45 (29.8)	13 (8.6)	5 (3.3)	88 (58.3)
Month 4	42 (27.8)	10 (6.6)	7 (4.6)	92 (60.9)
Month 5	43 (28.5)	7 (4.6)	4 (2.7)	97 (64.2)
Month 6	45 (29.8)	9 (6)	2 (1.3)	95 (62.9)

Table 5
Pain Management Pharmacologic Interventions

<i>Oral analgesics</i>	n (% of 151)
NSAIDs	18 (11.9)
Acetaminophen/opioid combinations	82 (54.3)
Short acting opioid	91 (60.3)
Long-acting opioid	73 (48.3)
<i>Parenteral analgesics</i>	n (% of 151)
Intravenous opioid (non-PCA)	141 (93.4)
Intravenous opioid (PCA)	89 (58.9)
Transdermal fentanyl	6 (4)
<i>Adjuvant medications</i>	n (% of 151)
Anticonvulsants (gabapentin)	76 (50.3)
Tricyclic antidepressants (amitriptyline)	19 (12.6)
Methadone (intravenous and oral)	6 (4)
<i>Local/regional anesthesia techniques</i>	n (% of 151)
LAWC (<i>Bupivacaine 0.2–0.5%</i>)	48 (31.8)
Continuous peripheral nerve blocks	4 (2.6)
<i>Bupivacaine 0.125%–0.2%</i>	2 (1.3)
<i>Ropivacaine 0.2%</i>	2 (1.3)
Epidural (lower extremity LSS)	n (% of 144)
<i>Bupivacaine (0.0625%–0.2%) plus fentanyl (2–10 mcg/ml)</i>	63 (43.8)
<i>Fentanyl (5mcg/ml)</i>	40 (27.8)
<i>Bupivacaine (0.1–0.125%) plus fentanyl (2–4 mcg/ml) plus clonidine (0.4 mcg/ml)</i>	8 (5.3)
<i>Levobupivacaine (0.0625%–0.125%) plus fentanyl (3–5 mcg/ml)</i>	7 (4.6)

Abbreviations: NSAIDs: Nonsteroidal anti-inflammatory drugs; PCA: Patient-controlled analgesia; LAW: Local anesthetic wound catheter; LSS: Limb-sparing surgery.