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Treatment of Sickle Cell Pain

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Abstract and Introduction

Abstract

Sickle cell disease affects 70,000 Americans who experience an average of 0.8 painful episodes each year. The pathophysiology of sickle cell pain is not completely understood. The disease is characterized by both acute and chronic pain syndromes. Patients with sickle cell pain often encounter barriers to receiving appropriate care, including lack of continuity of care and perceived opiate addiction. Studies describing pharmacotherapy for sickle cell pain have been primarily retrospective and uncontrolled. In analyzing the available literature regarding pathophysiology, assessment, and treatment of sickle cell pain, we found a need for increased practitioner education and inter-vention to improve the level of care provided to patients with this disease.

Introduction

Approximately 70,000 Americans have sickle cell disease, and 1000 babies are born with the disease each year.[1] Although sickle cell disease can be present in any ethnic group, it is most common in people of African ancestry.[2] The disease is characterized by episodes of pain. Patients experience an average of 0.8 pain episodes each year.[3] In fact, pain crises are the most common cause for hospitalization of patients with sickle cell disease, representing 75,000 hospitalizations and $475 million in health care expenditure annually.[2,4]

Pain is debilitating for many patients with sickle cell disease; however, not all patients experience pain episodes with the same frequency or intensity. In one survey, 38% of patients did not report a pain crisis during a 5-year evaluation period.[2] In fact, only a few patients experienced most episodes. Of the respondents, only 5% of patients experienced three or more painful episodes a year, but these represented approximately one-third of all episodes.[2] A correlation was reported between the number of pain crises and early mortality from sickle cell disease.[2] Patients with risk factors for poor pain control are those who have poor coping strategies or are poorly adjusted, those with adverse social situations, and those whose lives are more profoundly affected by their pain episodes.[5]

Many health professionals are reluctant to prescribe adequate dosages of opiates due to concerns regarding addiction and side effects.[6] An evaluation of adequacy of pain control in 21 children with sickle cell disease found that 71% had not achieved adequate pain control during the study period.[7] Three possible explanations were proposed: pain was inadequately assessed, choice or dosage of analgesic was inappropriate, or providers did not understand the nature of sickle cell pain.[7]

In March 1999, the Joint Committee on Accreditation of Healthcare Organizations (JCAHO) approved standards for assessment and management of pain for inpatients and outpatients. The standards stress that patients have a right to appropriate assessment and management of their pain. In 2000, JCAHO began to determine institu-tional compliance with pain management through interviews with patients, families, and clinical staff and through review of pain-related policies and procedures.[8]

Inadequate treatment of pain, new treatment standards, and increasing patient awareness of treatment alternatives all emphasize the need to improve the management of sickle cell pain crises. We reviewed the current literature on acute and chronic pain in patients with sickle cell disease by identifying clinical trials, case reports, and reviews in the Medline database from 1980-2001. Several other articles were identified through reference citations.

Pathophysiology and Presentation

Sickle cell pain is the result of tissue ischemia caused by occlusion of vascular beds with sickled erythrocytes. Under hypoxic conditions, hemoglobin S in the erythrocytes of patients with sickle cell disease reacts to form rigid polymers, leading to sickling or distortion of erythrocytes. Concurrently, polymorphonuclear leukocytes release cytokines, leading to expression of adhesion molecules on the vascular endothelium. These receptors bind passing erythrocytes.[9] The abnormal erythrocytes adhere to the vascular endothelium, which narrows the vascular lumen, traps more cells, and creates a hypoxic environment, encouraging further sickling.[10] In addition, interaction between erythrocytes and endothelium leads to release of vasoconstrictors, further inhibiting regional blood flow.[11] This cycle results in occlusion of certain vascular beds, most commonly in vertebrae, femur, hip, and ribs. Regional hypoxia can cause serious consequences, such as vascular necrosis of bone marrow or tissue infarcts. Acute inflammatory response to tissue injury may contribute to acute bone pain.[6,12]

Assessment

Acute sickle cell pain has been described as more severe than postoperative pain and as intense as cancer pain.[13] It is unpredictable and may be provoked by temperature extremes, changes in altitude, physical and emotional stress, dehydration, menstruation, fatigue, or infections. It may have no apparent precipitating factor. Fewer than 50% of patients can identify a precipitant.[14] The most common sites for pain are lower back, thigh, hip, knee, abdomen, and chest. Pain tends to recur in the same areas for individual patients and typically occurs in two or more sites at a time.[3] Bone pain is usually symmetric and bilateral. Abdominal pain mimics pancreatitis, cholecystitis, or appendicitis.[6] Episodes often begin at night[14]; they typically last 3-14 days and follow a pattern. Most patients are pain free between exacerbations; however, some experience a chronic pain syndrome. Many have prodromal signs, such as numbness, tingling, fatigue, or scleral icterus. Pain accelerates over several days, reaches a peak, and then declines to resolution or to baseline levels.[15,16]

A thorough history, physical examination, and review of systems should be conducted with each sickle cell pain crisis. Patients should be evaluated for possible precipitating factors and educated on avoiding triggers. Pain should be assessed as to quantity, quality, location, time course, and aggravating and alleviating factors. Various scales are available to help rate pain intensity; most common is the visual analog scale, which consists of a horizontal line labeled from 0 (absence of pain) to 10 (worst pain ever experienced). Patients should rate their current level of pain and compare it with their pain rating for an average day. A pediatric version of this scale incorporates photographs of African-American children displaying emotions ranging from happiness to neutrality to distress. Children are asked to point to the face that illustrates how they feel. Also, children who cannot describe the location of their pain may be able to mark on a drawing of a person the place that hurts on their own body.[13]

Few patients with sickle cell disease experience constant pain. However, one report describes sickle cell disease as a chronic pain syndrome with acute exacerbations.[17] Several sources of chronic sickle cell pain are aseptic necrosis, leg ulcerations, and bony infarctions. The goal of therapy for patients with chronic pain is to improve functional capability while decreasing the amount of pain experienced.[3] Chronic pain can be assessed by means of diaries in which patients record daily their pain rating, location of pain, and steps they took to control their pain.

Patients with sickle cell disease should be assessed at least once/year during pain-free periods to record characteristics of their acute and chronic pain (e.g., quality, quantity, aggravating and alleviating factors, effects on school or work activities). This is also an appro-priate time to discuss their response to various treatment methods and determine a pain manage-ment plan for their next crisis. Involving patients in planning encourages them to be more self-reliant and take an active role in their care.[3,13]

Barriers to Pain Management

Several psychosocial factors influence the management of sickle cell pain. First, and possibly most common, is the care provider's fear that the patient will become addicted to the prescribed analgesic. A survey of health care workers treating patients with sickle cell pain as well as other pain found that physicians and nurses perceived a much higher percentage of addiction than actually existed.[18] Undertreating pain because of fear of addiction predisposes patients to the development of pseudoaddictive behavior. This behavior is characterized by seeking and hoarding drugs due to fear of pain and usually disappears when pain is adequately managed.[19,20] Patient actions or attitudes that health care professionals may characterize as drug-seeking behavior may be best described as pain-avoidance behaviors.[19] Although many patients with sickle cell disease may complain of severe pain, they engage in activities that are inconsistent with the traditional image of the patient in severe pain, such as watching television or talking on the telephone. This is often perceived as exaggerating their pain to receive additional narcotics, whereas these activities may actually be learned distractions or coping mechanisms. Another example is the sleeping patient who, when awakened, reports unrelenting pain. Two points need to be addressed in this situation. First, this behavior pattern may be due to an imbalance between the sedative and analgesic effects of opiates.[21] Second, patients with pain still need to sleep; therefore, it is inappropriate to use this situation as an end point to decide if the patient is being truthful about the pain. Despite many health care workers' perceptions, the frequency of drug addiction in patients with sickle cell disease is only 1-3%.[6]

Communication barriers and lack of trust in the care provider also contribute to improper pain management. After experiencing suboptimal pain management, many patients develop a poor relationship with their providers. In a survey of more than 100 patients with sickle cell disease, most reported that their provider did not under-stand the amount of pain they experienced, and that they did not receive an analgesic drug when they needed it.[22] Many patients watch the clock or request an analgesic before administration time to ensure that they receive it promptly. Other patients who feel dependent on the health care system for pain control may display immature behavior, somatic complaints, hostile withdrawal, abusiveness, and dependency.[23] Patient age may also affect communication regarding pain. A comparison of pain ratings by children and adolescents found that children tended to report less pain.[24]

The type of institution providing care to patients with sickle cell disease also affects pain management. A survey of patients revealed that a system of inpatient admissions for treatment of pain encouraged dependence on inpatient care and discouraged self-reliance.[22] Many patients are treated at teaching institutions and interact with many residents, interns, and attending staff at each admission. Each physician approaches pain control in a different way, which results in various levels of care.[19,23] Some specialists advocate sickle cell teams who follow patients continually. Continuity of care could result in better patient-provider relationships and more individual care based on patient history.[6,25]

Some institutions report success with day treatment centers specializing in sickle cell pain crises. In one, 80% of patients went home after treatment; average length of stay was 4-5 hours. The inpatient admission rate was only 8.3% versus a previous rate of 42.7% based on emergency department treatment.[26] Therapy is determined through a combination of treatment algorithms and the patient's pain history. Center management of pain crises may involve intermittent intravenous injections, patient-controlled analgesics, hydration, and adjunctive therapies.

Despite these advances, most patients still are treated in emergency facilities and as inpatients. Patients report long waiting periods before they are assessed in emergency facilities. Emergency departments could improve continuity of care by maintaining patient records describing medical history, drug therapy, and usual pain treatments.[19,23] Although this approach has been widely suggested, it has not been evaluated in a controlled manner.

Treatment Modes

Routes of Drug Administration

Most physicians in sickle cell centers prefer the intravenous route for providing analgesics.[27] Administering analgesics as needed is not appropriate for sickle cell pain because the pain is sustained; however, scheduled fixed doses do not address the variability seen in patients with sickle cell disease.[3,6] For sickle cell pain, patient-controlled administration of an analgesic drug is equal in efficacy to intermittent dosing. Patient-controlled

administration can decrease nursing time, shorten time between pain perception and drug administration, and lower patient anxiety.[28]

Several concerns limit intramuscular administration of an analgesic. Although it may be useful before intravenous access is obtained, repeated intramuscular injections may result in muscle damage and formation of sterile abscesses. An evaluation of pharmacokinetics of meperidine after intramuscular administration reported a 2- to 3-fold variation in time to peak.[14] Thus, the intramuscular route should be avoided whenever possible.

Oral analgesics for treating sickle cell pain crises have not been evaluated extensively but have met with some success. One study that evaluated intravenous versus oral morphine in children with vasoocclusive episodes found equal efficacy and safety in both groups.[29] In another study, oral morphine was administered in combination with a nonsteroidal antiinflammatory agent for treatment of acute pain episodes in an emergency department. Compared with historical controls, admission rates decreased with this treatment.[30] In most cases the oral route should be reserved for patients with mild-to-moderate pain or those in the latter stages of recovery who can tolerate oral intake. Physicians may find intravenous or patient-controlled bolus doses useful as a bridge to conversion to oral therapy.[3] Patients who are discharged receiving oral therapy should be provided with enough drug to last until their follow-up appointment.

Transdermal fentanyl has been suggested as an alternative for both acute and chronic pain control. Transdermal administration has two potential drawbacks. First, it takes 12 hours to achieve steady state, and patients still require treatment for breakthrough pain. Second, titrating the dosage to the patient's fluctuating pain is difficult.[14] However, the transdermal route might be effective when venous access is difficult.

Epidural pain control may be an alternative route for patients with acute pain that is unresponsive to other routes and adjunctive therapies. Epidural pain control could avoid some side effects of intravenous or patient-controlled administration of opiates. Epidural administration is most effective when the pain is located below the fourth dermatome.[3,31]

Table 1 summarizes several studies evaluating different opiates and routes of administration.[19,28-30,32-35]

Drugs Administered

Opiates. Most opiates have comparable efficacy and safety profiles, making them difficult to differentiate.[3] Morphine is considered the drug of choice for treatment of acute sickle cell pain crisis.[6] However, morphine's pharmacokinetics, and thus dosing, vary among patients.[7] One study of patients with sickle cell disease reported an 8-fold variation in morphine clearance (6.2-59.1 ml/min/kg).[36] Patients with sickle cell disease have more rapid plasma clearances and shorter half-lives for morphine than other patients, such as those with cancer and those undergoing surgery. In addition, patients with severe symptoms have significantly faster clearances than those with moderate symptoms (23.4 ml/min/kg and 36.3 ml/min/kg, respectively, p=0.042).[36] More rapid clearance may result in a weaker analgesic response from commonly administered doses.[36]

Meperidine often is the opiate of choice for patients with sickle cell pain crisis; however, its use has been discouraged due to the risk of seizures. In fact, this patient population may be particularly vulnerable to seizures because of reduced renal function, high meperidine dosages, and altered meperidine pharmacokinetics.[3,27] The drug's short half-life requires frequent dosing to maintain adequate levels of analgesia. One pharmacokinetic evaluation found that patients with sickle cell disease had significantly lower meperidine levels at all time points than a control group of patients with abscesses.[37]

Hydromorphone has fewer side effects than morphine and may be an alternative for patients who experience nausea or pruritus with morphine.[3] However, no controlled studies have evaluated administration or pharmacokinetics of hydromorphone in this patient population.

Administration of an agonist-antagonist drug for patients with acute sickle cell pain is controversial; however, the efficacy of nalbuphine has been evaluated in children with sickle cell disease. A retrospective chart review of nalbuphine versus meperidine in 16 children and young adults found that pain control with nalbuphine was similar to that achieved with meperidine.[7,38] However, some practitioners question whether administration of an agonist-

antagonist drug is ethically appropriate considering the severity of sickle cell pain.[7] Another concern is the possible development of a withdrawal-like syndrome in patients receiving long-term therapy with opiate agonists.

Oral opiates such as methadone, morphine, codeine, oxycodone, and hydroxycodone provide alternatives for outpatient treatment and pain management for patients discharged from the hospital. Although these drugs are administered routinely to patients with sickle cell disease, their efficacy and safety have not been evaluated for treatment of acute pain crisis. These drugs are given as an oral analgesic for treatment of mild-to-moderate pain at home, as transitional therapy between hospital treatment and home manage-ment, or for management of chronic pain.

Adjunctive Therapy for Acute Pain. Several adjunctive treatments have been used as combination or primary therapy for acute episodes of sickle cell pain. Nonsteroidal antiinflammatory agents such as ketorolac, piroxicam, and ibuprofen have been evaluated for monotherapy and in combination with opiates for vasoocclusive crises. Ketorolac is a successful primary treatment for patients unable to tolerate opiates.[7,39] In a blinded, crossover trial with 20 children, ketorolac provided superior pain control and with fewer side effects than meperidine.[7,39,40] Another report evaluated the effects of a single dose of ketorolac given to patients in an emergency department. These patients received no less narcotic therapy than their counterparts, but continued ketorolac administration may have provided increased benefit.[41] No significant difference was found between patients with sickle cell pain treated with a combination of a single dose of ketorolac in addition to morphine and a control group receiving morphine as monotherapy.[42] The group receiving ketorolac and morphine experienced the same degree of pain, rate of hospital admission, and total opiate dose as the morphine monotherapy group.

A more recent study evaluated efficacy of intravenous ketorolac for treatment of acute sickle cell crises in a pediatric emergency department.[43] In 70 episodes treated, more than half resolved with ketorolac and fluids only. An initial pain score greater than 7 out of 10 or the presence of four or more pain sites were predictors of failure of monotherapy with ketorolac. A Nigerian trial found that piroxicam for treatment of vasoocclusive crisis was as effective as aspirin and had fewer side effects.[44] Ibuprofen was suggested as an addition to traditional pain management regimens.[30] However, possible detrimental effects of nonsteroidal antiinflammatory agents on bone healing is a concern.[3] Although these agents should address the inflammatory component of sickle cell pain, further study is needed to evaluate the best role for them in treatment of acute sickle cell crises.

Methylprednisolone was administered with standard therapy in a randomized, double-blind trial involving 56 episodes of pain crisis in children and adolescents.[45] In the steroid group, in which patients received methylprednisolone 15 mg/kg up to a maximum dose of 1000 mg, the duration of inpatient analgesic therapy was significantly reduced compared with the placebo group. However, the steroid group experienced more recurrences of pain than the placebo group shortly after therapy was completed. No adverse effects were reported. As with nonsteroidal antiinflammatory drugs, effects of glucocorticoid agents on bone healing and frequency of avascular necrosis are of concern.[3]

Stimulants have been suggested for adjunctive therapy in acute pain crises. Methylphenidate and dextroamphetamine are thought to have intrinsic analgesic properties and may enhance analgesia provided by opiates. They also may counteract some of the somnolence associated with opiates, allowing for administration of higher dosages of analgesics.[3] These agents have not been evaluated in a controlled manner for patients with sickle cell pain.

Tricyclic antidepressants and anticonvulsants are given for various pain syndromes, including neuropathic pain, and they have been included in several reported treatment protocols. However, their efficacy has not been directly evaluated for treatment of acute and chronic sickle cell pain.[3]

Providing adequate hydration is a component of almost every treatment protocol for vasoocclusive crises. Dehydration is one of the principal precipitating factors for pain crises. However, overcorrection of fluid balance can have a negative effect, including possibly increasing the risk of acute chest syndrome. This syndrome, characterized by cough, chest pain, dyspnea, fever, and radiographic changes, is the most common cause of death for patients with sickle cell disease.[3,46] Hydration should be provided to correct deficits, replace any ongoing losses, and maintain euvolemia. Mild pain may improve with oral hydration.[6]

Both psychological and behavioral therapies have been provided as adjuncts to traditional analgesics. Psychological strategies include distraction, guided imagery, hypnotherapy, psychotherapy, and patient education

about pain.[3] An evaluation of a program to teach coping skills (breathing, relaxation, and distractions) found that when patients used coping skills, their use of health care resources decreased. However, the benefit of instruction decreased without reinforcement.[47] Behavioral techniques may include relaxation, biofeedback, behavior modification, and deep breathing exercises.[3] Pain-behavior contracts, which have been used mainly with patients whose actions are perceived as inappropriate, may provide a way to define limits and expectations for patient and care provider and may place responsibility on the patient for adhering to the treatment plan. These contracts can be used with adolescents and adults to decrease maladaptive behaviors, improve compliance with care plans, and maximize pain control. Contracts can address types of analgesics to be administered; compliance with other interventions, such as incentive spirometry; and activities of daily living, such as remaining mobile.[22,27] No randomized trials have been performed to evaluate their efficacy.

Preventive Therapy

Polymerization of hemoglobin S is dependent on its concentration. Other types of hemoglobin, specifically fetal hemoglobin (hemoglobin F), are resistant to sickling. Hydroxyurea, the most recent advance in prevention of the sequelae of sickle cell disease, increases the concentration of hemoglobin F in erythrocytes. Hemoglobin F forms soluble polymers with hemoglobin S, reducing the overall concentration of hemoglobin S and the likelihood of polymerization and sickling of the cell. Hydroxyurea causes significant reduction in the incidence of acute pain crises (from 4.5 to 2.5 crises/year, $p<0.001$), acute chest syndrome (from 51 to 25 episodes/ year, $p<0.001$), and need for transfusions (from 73 to 48 transfusion/year, $p=0.001$).[48]

Hydroxyurea has been evaluated for use in adult and pediatric populations.[48-50] In most protocols, hydroxyurea is started at 10-15 mg/kg and then titrated to an effective dosage. Efficacy is evaluated by monitoring for an increase in hemoglobin F concentrations or mean corpuscular volume.[11] Dosages are titrated over several months, with monitoring of complete blood counts every 2 weeks at the start of therapy and then regularly throughout therapy. Efficacy of hydroxyurea depends on patient adherence to the treatment regimen and on close monitoring for side effects such as myelosuppression.[10,11,48]

Future Therapy Options

Although further research is needed to evaluate existing modes of therapy, most research focuses on preventive therapy. Different therapies are being investigated. Levels of the inflammatory neuropeptide substance P are elevated in patients with sickle cell disease and increase further during pain crises. Substance P induces vaso-dilation, plasma extravasation, release of histamine from mast cells, and release of inflammatory mediators such as interleukins and tumor necrosis factor. Therefore, neurokinin antagonists may have a role in treating or preventing pain episodes.[51] Phase III trials have been completed for poloxamer 188 (Flocor; CytRx Corp., Atlanta, GA), which decreases length of crises by improving microvascular blood flow.[52] In addition, effects of leukotriene antagonists on frequency and severity of pain crises are under investigation (Haynes J, College of Medicine Research Office, University of South Alabama, Mobile, AL, personal communication, July 2001).

Conclusions

Acute and chronic sickle cell pain present many therapeutic challenges. Specific knowledge of the disease state, altered pharmacokinetics of opiates, and adjunctive therapies allow clinicians to improve treatment of their patients' pain. Institutions serving patients with sickle cell disease would be well advised to develop a protocol for acute management of these patients. Centers with many such patients should evaluate the feasibility of treatment through clinics. Algorithms must address choice of analgesic and route, hydration, and administration of nonsteroidal antiinflammatory drugs. Many effective alternatives for pain control are available for management of sickle cell pain.

Studies describing pharmacotherapy for sickle cell pain have been primarily retrospective and uncontrolled; only a few have compared opiates, and very little difference in their efficacy and safety has been reported. However, meperidine should be avoided if possible, considering its altered pharmacokinetics and the risk of associated adverse effects. A protocol-guided approach to acute pain crises consistently has improved patients' satisfaction with their care. Those with frequent hospital admissions may benefit from a pain-behavior contract to promote more consistent care. Clinicians must manage acute and chronic sickle cell pain aggressively to improve their patients' quality of life.

Table 1. Studies Evaluating Opiates and Administration Routes for Patients with Sickle Cell Pain

Patients	Study Design	Drug, Route of Administration	Dosage	Results
38 children[19]	Retrospective review of 98 hospital admissions	Morphine or meperidine, i.v.	Morphine 0.15-mg/kg bolus, then 0.07-0.1 mg/kg/hr Meperidine 1-mg/kg bolus, then 0.5-0.7 mg/kg/hr	Patients reported better pain control with the protocol than with previous random treatment by physician.
20 adults[28]	Randomized	Morphine, PCA vs intermittent injection	PCA group: 2-mg bolus with 1 mg PCA and 6-min lockout; may increase to 1.5 mg PCA Intermittent injection group: 4 mg every 30-60 min; may increase to 6 mg	No significant difference in amount of morphine given (28.8 ± 13 mg vs 25.5 ± 23.5 mg), length of stay (6.5 ± 2.6 hrs vs 7.1 ± 3.6 hrs) or side effects (53% vs 47%) for intermittent group and PCA group, respectively.
66 children[29]	Randomized, placebo-controlled	Morphine, i.v. vs p.o.	Group 1: 0.15 mg/kg i.v., then 1.9 mg/kg sustained- release tablets every 12 hrs, with immediate-release tablets for breakthrough Group 2: 0.15 mg/kg i.v., then continuous at 4 mg/kg/hr, with i.v. bolus for breakthrough	No significant difference in pain scores (6.3 vs 6.4), duration of opiate administration (4.2 vs 5.4 days), or side effects for p.o. and i.v., respectively.
9 patients[30]	Retrospective review of 116 emergency visits over 1 yr	Morphine, p.o.	Elixir 60 mg, then 20 mg every 30 min until pain relief or sedation over 6-8 hrs, then admit or discharge, vs i.v. meperidine	Fewer emergency visits (150 vs 116, p<0.01) and hospital admissions (19 vs 5, p<0.01) with protocol.
26 children and adolescents[32]	Retrospective review of 60 hospital admissions	Morphine, PCA	Group 1: PCA dose of 0.25 mg/kg, basal at night 0.01-0.03 mg/kg/hr, 1-hr limit of 0.1-0.15 mg/kg Group 2: PCA dose of 0.1-0.2 mg/kg, continuous basal 0.05-0.2 mg/kg/hr, 1-hr limit of 0.05-0.2 mg/kg	Group 1 received significantly less than group 2 (6681 vs 10,667 mg, p=0.013) and had fewer PCA days (4.9 vs 6.16, p=0.0112) and hospital days (5.033 vs 7.183, p=0.0012); no difference in side effects.
66 children[33]	Randomized, placebo-controlled	Opiates, intermittent vs continuous	Group 1: Morphine, codeine, or meperidine, bolus every 3-4 hrs Group 2: Morphine 0.004 mg/kg/hr	No difference in mean dosage (0.032 vs 0.035 mg/kg/hr), significant reduction in duration of severe pain in continuous group (2 ± 1.8 days vs 0.9 ± 1 day), no difference in side

				effects.
50 adults[34]	Case series, switch from meperidine to morphine	Morphine, i.v.	5-mg bolus, then 5 mg/hr with unspecified bolus dose, discharged with extended-release	Emergency visits decreased by 67%, length of stay by 23%; admissions to other hospitals did not increase.
45 adults[35]	Randomized, double-blind	Morphine vs butorphanol, i.m.	Morphine 6 mg or butorphanol 2 mg every 30-60 min	No significant difference in pain relief, discharge rates (68.6% vs 68.2%), or frequency of adverse effects (13% vs 23%).

PCA = patient-controlled analgesia.

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