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Pain in children with sickle cell anemia

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Pain in Children with Sickle Cell Anemia

by

Eufemia Jacob

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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NURSING

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GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Dedication

To the children
with sickle cell disease and their families

To the nurses
at the Hematology/Oncology Unit
at Children's Hospital Oakland

To my parents
Honoraria Jacob and Delfin Jacob

To my seven sisters and their families
Josie and David De Los Reyes
Annemarie, Mark, Florence, and Gabriel De Los Reyes

Belinda Jacob and Tommy Sablan

Sonia Jacob and Kenneth Greenwood
Nicole, Brandon, and Lauren Greenwood

Cecilia Jacob
Matthew and Ehren Serrano

Evangeline and Andre Shkidt
Sarah and Michael Shkidt

Zaida and Kavindra Patel
Vasean, Rajiv, and Julia Patel

Agnes Jacob and George Hines
Mia Sophie Jacob Hines

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ABSTRACT

Pain in Children with Sickle Cell Disease
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A longitudinal study was used to examine the multidimensional aspects of pain in children with sickle cell disease who were hospitalized for painful vaso-occlusive episodes. Not only were changes in pain intensity, pain location, and pain quality evaluated from the day of admission through the day of discharge, but changes in functional status, such as sleeping, eating, and activity during hospitalization were also evaluated. In addition, clinical signs and symptoms associated with vaso-occlusive painful episodes and CBC values were examined in relation to the pain experience during hospitalizations. Relationships between pharmacologic interventions and children's self-reports of pain relief, and between pharmacologic interventions and pain characteristics during hospitalization were also analyzed. The UCSF Symptom Management Model was used as the conceptual framework, which focused on three interrelated dimensions: pain experience, pain management, and pain outcomes.

Data were collected once every evening from day of admission to the day of discharge from the Hematology/Oncology Unit, Children's Hospital Oakland. Participants were hospitalized children with sickle cell disease, age 5 to 19 years, with admitting diagnosis of vaso-occlusive pain. Children included were English-speaking, who assented to participate and whose parents consented, and did not have prior history

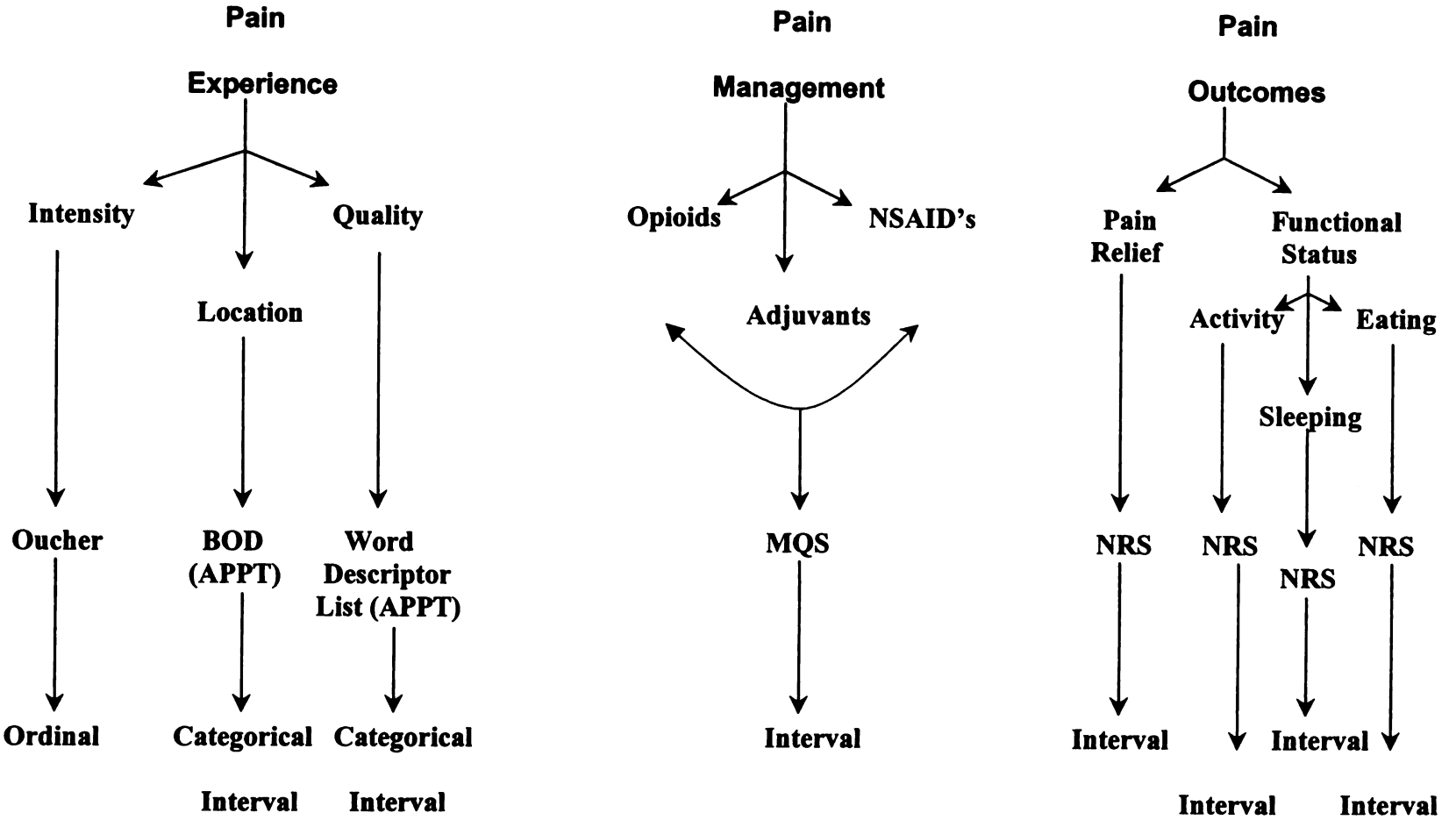
of neurological impairments (i.e. visual or hearing deficits, learning disability, motor function deficit, and developmental delay).

A wide inter-individual variability in the pain experience in this sample of children with sickle cell disease who were hospitalized for painful episodes, suggests that pain management strategies need to be individualized. Pain management strategies need to be titrated to effect according to individual needs. Low analgesic use may have lead to poor outcomes of little relief and minimal functional status. Clinicians may need to evaluate responses to treatment more frequently, titrate medications to effect as recommended by the APS Guidelines for Management of Pain in Sickle Cell Disease, and encourage patients to use the amount of medications prescribed so that their relief can be maximized. Clinicians need to provide ongoing education as necessary to remind patients of the negative consequences related to unrelieved pain and that the risks of negative outcomes are higher than the risks of addiction.

Christine Miaskowski, RN, PhD, FAAN

THE UCSF SYMPTOM MANAGEMENT MODEL

Conceptual Framework for Research on Pain in Children with Sickle Cell Disease



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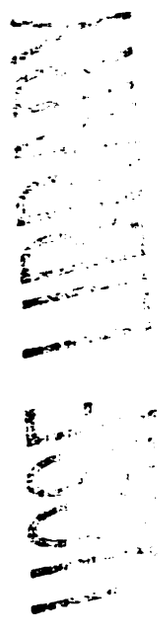


CHAPTER 1

INTRODUCTION

Sickle cell disease is a genetic disorder that affects one in six-hundred African American infants in the United States. The normal adult hemoglobin (hemoglobin A--HgbA) is partly or completely replaced by abnormal sickle hemoglobin--HgbS. An individual inherits the sickle hemoglobin (HgbS) gene from both parents (homozygous). Heterozygous individuals (abnormal gene inherited from only one parent) are said to have the sickle cell trait. They are generally asymptomatic and have a normal life span (Baldy, 1997).

The hemoglobin of patients with sickle cell disease differs electrophoretically from the hemoglobin of normal individuals. The hemoglobin of individuals with the asymptomatic sickle cell trait appears to be a mixture of normal and abnormal hemoglobin (Pauling, Itano, Singer, & Wells, 1949). The red blood cells (RBC) of a person with sickle cell disease (HgbSS) generally contain between 80% and 100% hemoglobin S (HgbS). In persons without sickle cell disease, normal hemoglobin A (HgbA) makes up over 95% of the hemoglobin. Some people have the sickle cell trait (HgbAS), where the proportion of HgbS is between 45% and 55%. This percentage is generally too low to cause sickling and cells will only sickle under certain extreme conditions (Baldy, 1997). Other electrophoretically abnormal hemoglobins were identified that do not cause sickling, such as HgbC, but which were found in association with HgbS in a patient with a mild form of sickle cell disease (Itano & Neel, 1950). Formal genetic analyses of families, showed that both parents of children with sickle cell disease have the sickle cell trait (Neel, 1951).

STATEMENT OF THE PROBLEM

The most urgent and alarming symptom in a child with sickle cell disease is the painful episode that accompanies a vaso-occlusive event (Shapiro & Ballas, 1994). Vaso-occlusion occurs when the RBCs, which are normally smooth and flexible, become stiff and deformed into an elongated, or sickle shape. The lifespan of these RBCs is reduced from 120 days to 6 to 10 days (Baldy, 1997). The viscosity of the blood increases, and the RBCs become trapped in the inner layers of blood vessels and adhere to the vessel walls. Eventually blood flow to the tissues is obstructed, followed by ischemia, swelling, pain, damage to the tissues, and infarction (Midence & Elander, 1994).

The painful episode is one of the most characteristic manifestations of sickle cell disease. It usually consists of pain in the extremities, back, abdomen, or chest. Mild and unilateral, or severe and migratory joint effusions may also accompany a painful episode. Joint effusions result from necrosis of marrow that is adjacent to the synovial membranes or from congestion and vascular thrombosis of the small vessels of the synovium (Brugsch & Gill, 1944; DeCeulaer, Forbes, Roper, & Serjeant, 1984; Espinoza, Spilberg, & Osterland, 1974; Mallory, 1941; Schumacher, 1975; Schumacher, Andrews, & McLaughlin, 1973; Serjeant, 1992).

Ischemia, infarction, and inflammation may be responsible for initiating the painful episode (Charache & Zohoun, 1987). These signs reflect the accumulation of inflammatory mediators such as bradykinin and substance P that are known to cause local pain, vasodilatation, extravasation of fluids, and edema (Miller, Webster, & Melmon, 1975). The painful episode is usually associated with fever, which may reflect the

inflammatory process and the passage of dark or red urine, which may reflect increased urinary porphyrin excretion as a result of the breakdown of RBCs (Neumann, Diggs, Schlenker, & Barreras, 1966).

The painful episode generally results from avascular necrosis of the bone marrow (Serjeant, 1992). Changes in the bone marrow that accompany a painful episode may include: necrosis, increased calcium turnover, decreased bone marrow blood flow, fibrosis which may become permanent, infarction, edema, increased fat, and erythropoiesis (Alavi, Bond, Kuhl, & Creech, 1974; Charache & Page, 1967; Diggs, 1967; Hammel, DeNardo, DeNardo, & Lewis, 1973; Hutchinson, Merrick, & White, 1973; Majd & Frankel, 1976; Rao & Patel, 1989; Rao et al., 1986; VanZanten, Eps, Golding, & Valk, 1989). Necrotic bone marrow, fat, and spicules of bone may occur as emboli in the small vessels of the brain, lungs, or kidneys (Brittingham & Phinizy, 1931; Chmel & Bertles, 1975; Diggs, Pulliam, & King, 1937; Evans & Symmes, 1957; Ober, Bruno, Simon, & Weiner, 1959). Patients experience severe back pain, chest tightness, dyspnea, and falling arterial oxygen tension. They may show signs of systemic embolism involving the respiratory, renal, and central nervous systems (Serjeant, 1992).

Painful episodes are most common in patients with high hemoglobin levels and high reticulocyte counts (Baum, Dunn, Maude, & Serjeant, 1987; Platt et al., 1991). Total hemoglobin levels and unconjugated bilirubin levels decrease during the painful episode in most patients, while reticulocyte counts may increase in some patients (Billett, Nagel, & Fabry, 1988; Fabry, Benjamin, Lawrence, & Nagel, 1984; Warth & Rucknagel, 1984). Painful episodes are also more frequent in patients with greater red cell deformability, indicating the cells' tendency to readily attach to endothelium (Ballas, 1991; Ballas et al.,

1988; Billett, Kim, Fabry, & Nagel, 1986; Lande et al., 1986; Mohandas & Evans, 1985). Total sickle cell counts may or may not change during a painful episode (Barreras & Diggs, 1964; Diggs, 1956; Richardson, Breeze, & Stuart, 1976; Rieber, Veliz, & Polack, 1977; Westerman & Bacus, 1983). Leukocyte counts increase, with a marked increase in band neutrophils when infection is present. In the absence of infection, the increase in leukocyte counts is presumed to reflect an inflammatory response to necrotic bone marrow (Buchanan & Glader, 1978; Diggs, 1965). Platelet counts and fibrinogen levels may or may not change during the course of the painful episode (Serjeant, 1992).

Infections, fever, dehydration, and acidosis can precipitate a painful crisis (Diggs, 1965; Edington, 1953; Hendrickse, 1965; Hendrickse & Barnes, 1966; Konotey-Ahulu, 1971a; Koonotey-Ahulu, 1971b; Lecocq & Harper, 1963; Lewthwaite, 1962; Margolies, 1951; Nwokolo, 1960; Paterson & Sprague, 1959; Warley et al., 1965; Wright & Gardner, 1960). Some patients with frequent painful crises showed a fall in oxygen saturation during sleep, which is associated with a reduced tidal volume (Castele, Strohl, Chester, Brittenham, & Harris, 1986; Scharf et al., 1983; Sidman & Fry, 1988). Other factors such as altitude (Claster, Godwin, & Embury, 1981; Mahoney & Githens, 1979), emotional distress (Nadel & Portadin, 1977), excessive sweating, exercise, alcoholic intoxication which may cause dehydration (Diggs, 1965), and diuresis may also precipitate painful episodes (Sweeney, Dobbins, & Etteldorf, 1962). Exertion can also decrease the level of oxygen in the blood and cause acidosis. Dehydration can lead to reduced plasma volume, increased blood viscosity, and can interfere with blood flow. Respiratory infections can cause deoxygenation of the sickled hemoglobin, and fever or

high temperature increases the tendency of RBCs to sickle. Cold exposure decreases blood flow, as vasoconstriction occurs in small vessels (Shapiro & Ballas, 1994).

Phases of a Painful Episode

The phases of a painful episode have been characterized to only a limited extent (Akinola, Stevens, Franklin, Nash, & Stuart, 1992; Ballas & Smith, 1992). There are some data to suggest that a prodromal or preepisode phase occurs in both children and adults. Three additional phases and a potential relapse phase have been identified in adults (Akinola et al., 1992; Ballas & Smith, 1992). In children, eight phases have been suggested (Beyer, et al, 1998). Four phases occurred prior to hospitalization and four phases occurred during hospitalization.

Prodromal or Preepisode Phase

Diggs (1965) first reported on the premonition of a painful episode (i.e., the prodromal, premonitory, or preepisode phase). One mother could predict when her child would develop a painful episode by noting that the fingers were pale. Murray and May (1988) reported that 59 out of 102 patients experienced a prodromal phase to the painful episode that occurred up to 24 hours before developing features typical of the episode. Numbness, aches, and pins and needles sensations in the areas subsequently affected were reported and the duration of the prodromal phase was commonly up to 24 hours. Akinola and colleagues (1992) studied 20 patients with sickle cell disease, who were visited regularly at home by a nurse practitioner and were taught to keep a diary of clinical events. Twelve of 14 premonitions were followed by a typical painful episode that required either home treatment or hospitalization.

Decreased RBC deformability, increased number of both dense RBCs, and irreversibly sickled cells (ISC) were found during the prodromal phase (Akinola et al., 1992). The prodromal phase may possibly mark the onset of necrosis and the pain reflects the inflammatory response. If the prodromal episode can be well characterized, it may offer an avenue to abort an evolving episode or to prevent the propagation of painful episodes, by initiating preemptive analgesia (Katz, Kaanagh, & Sandler, 1991; McQuay, 1992). However, some painful episodes do not have identifiable triggers and are unpredictable (Shapiro & Ballas, 1994).

Data on the Phases of the Painful Episode in Adults

A limited amount of research has characterized the phases of the painful episode in adults. A typical painful episode in adults lasts an average of 10 days (Davies, 1990) and evolves along three distinct phases (Akinola et al., 1992; Ballas & Smith, 1992).

Phase I. In phase one, pain escalates to a maximum in the evolving phase (also called the infarctive phase). The following changes in the blood occur: a decrease in erythrocyte deformability; an increase in the percentage of dense cells in the circulation; and an increase in RBC distribution width (RDW) and hemoglobin distribution width (HDW) (Akinola et al., 1992; Ballas, 1991; Ballas et al., 1988; Ballas & Smith, 1992; Billett et al., 1988; Fabry et al., 1984; Lawrence & Fabry, 1986; Serjeant, Serjeant, & Milner, 1969). The increase in dense RBC's may be relative and secondary to preferential trapping of deformed discoid cells in the microvasculature and to the formation of new irreversibly sickled cells. Anemia worsens, but it may not be recognized without baseline counts (Ballas & Smith, 1992). The pain increases gradually

in severity and peaks by the second or third day of the episode. Fear, anorexia, and anxiety usually are present during this phase (Ballas, 1990; Diggs, 1965).

Phase II. The second phase is the established phase (also called the postinfarctive or inflammatory phase) which typically lasts four to five days. Persistence of severe steady pain and signs and symptoms of inflammation such as fever (Ballas et al., 1988; Diggs, 1965; Samuels-Reid & Scott, 1985), leukocytosis (Akinola et al., 1992; Billett et al., 1988; Buchanan & Glader, 1978; Diggs, 1965), swelling, tenderness, and joint effusions (Ballas et al., 1988; Schumacher, 1975; Serjeant, 1992) predominate. Other changes include: a marked increase in serum levels of acute-phase reactants, such as C-reactive protein and serum amyloid (Akinola et al., 1992; Becton, Raymond, Thompson, & Berry, 1989; Lawrence & Fabry, 1986); signs of hemolysis, (i.e., decreased hemoglobin, increased reticulocyte count); increased levels of lactate dehydrogenase (LDH), a sign of tissue damage and bone marrow infarction; and increased levels of creatinine phosphokinase (CPK) indicating skeletal muscle injury (Billett et al., 1988).

Phase III. The third phase is the resolving phase (also called the healing, recovery, or postepisode phase). This phase is accompanied by a gradual decrease in pain severity and may last one to two days. Common features of this phase include: an increase in RBC deformability; a decrease in the percentage of dense cells; a decrease in RDW and HDW; a decrease in the number of irreversibly sickled cells; and a return of hemoglobin and reticulocyte counts to their preepisode levels (Ballas, 1991; Ballas et al., 1988; Ballas & Smith, 1992; Serjeant et al., 1969). Changes in RDW and HDW are proposed to be a simple method to track the progression of a painful episode (Shapiro & Ballas, 1994).

Relapse. Rebound thrombocytosis and an increase in acute-phase reactants, particularly fibrinogen and α-1acid glycoprotein or osmomucoid, may occur during relapse. Plasma viscosity and erythrocyte sedimentation rate (ESR) increase above baseline values. In 20% of adults with sickle cell disease, painful crises may recur within one week of resolution of previous painful crises. This recurrence may be related to an increased level of deformable cells that are potentially capable of adhering to endothelial cells of the microvasculature, and eventually blocking the microcirculation (Ballas & Smith, 1992). The increased reticulocyte count during the resolving phase could increase the number of young reticulocytes expressing the $\alpha_4\beta_1$-integrin complex (Swerlick, Eckman, Kumar, Jeitler, & Wick, 1993). The $\alpha_4\beta_1$-integrin complex binds to activated endothelial cells by interacting with erythrocyte $\alpha_4\beta_1$ and endothelial cell vascular cell adhesion molecule-1 (VCAM-1). This interaction together with other changes in plasma, such as increased plasma viscosity, as well as increases in fibrinogen levels, platelet counts, and intercellular adhesion molecule-1 (ICAM-1) levels may contribute to a further predisposition toward vascular occlusion in the resolving phase of the episode (Blei, Guarini, & Carriero, 1993).

Data on the Phases of the Painful Episode in Children

Beyer, Simmons, Woods, and Woods (1998) interviewed 21 children and adolescents (6 to 15 years) and their family caregivers, once during a painful episode, and once when the child was not experiencing a painful episode. From these interviews, a chronology of pain and comfort emerged in which the progression of vaso-occlusive pain and the use of specific comfort measures occurred in eight distinct phases. Four phases occurred prior to hospitalization, and four phases occurred during hospitalization.

Phase I (baseline) represented the child's usual state, when there was no pain. In ***Phase II*** (pre-pain phase), the child showed no evidence of pain but began to display some prodromal signs and symptoms (e.g., yellow eyes, fatigue) of vaso-occlusion. In ***Phase III*** (pain startpoint), the child complained of mild "ache-ish" pain in one specific area, which gradually or rapidly increased or "waxed". ***Phase IV*** (pain acceleration) occurred when pain continued to escalate. Pain intensity increased from mild to moderate and appeared in more areas of the body. A decreased level of activity as well as differences in behaviors, appearance, and mood were observed (Beyer, et al, 1998).

In ***Phase V*** (peak pain experience), pain continued to escalate and in some cases, children were incapacitated and unable to get pain relief. Pain was described by children as "stabbing", "drilling", "pounding", "banging", "unbearable", or "throbbing". Caregivers sometimes made the decision to seek emergency room help for stronger analgesics and protection from complications such as fever or respiratory distress. Pain often increased despite all efforts, and the decision was made to take the child to the emergency room. ***Phase VI*** (pain decrease startpoint) occurred when pain began to resolve after the use of intravenous (IV) fluids and analgesics, which sedated the child and allowed the child to sleep for longer periods. Pain began to decrease slightly but it was still sharp and throbbing. ***Phase VII*** (steady pain decline) occurred when the child's pain decreased slowly or rapidly. The child increased his or her activity level. Mobility was improved, pain levels were reported as "just a little", and more animation in behaviors was evident. In ***Phase VIII*** (pain resolution), pain was at tolerable levels and the child was often discharged from the hospital on mild oral analgesics. Some children

reached baseline conditions with behavior, appearance, and mood more normal and with fewer complaints of pain (Beyer, et al, 1998).

In summary, clinical signs and symptoms, laboratory data, and CBC values (Akinola et al., 1992; Ballas & Smith, 1992) show predictable changes as a painful episode unfolds in adults. However, these changes have not been documented in children. Findings from one study in children (Beyer, et al, 1998) suggest that clinical signs and symptoms of vaso-occlusion and pain occur in phases. No other studies were found that described predictable changes or phases of sickle cell pain in children. In the study by Beyer and colleagues (1998), pain intensity was not quantified during each phase. In addition, other characteristics of pain (e.g., location, quality), changes in functional status (e.g., sleep, activity, eating), signs and symptoms of vaso-occlusion and inflammation, and changes in CBC values were not described for each of the phases. Furthermore, changes in pain management strategies and children's self-reports of the effectiveness of these strategies as the painful episode evolved were not examined.

SIGNIFICANCE

A guiding principle in pain management is that prevention is always better than treatment. Pain that is established and severe is often more difficult to control and more difficult to suppress (McQuay, 1989; Wall, 1988; Woolf & Wall, 1986). When pain is untreated, sensory input from injured tissues reaches spinal cord neurons and may cause subsequent responses to be enhanced. Long-lasting changes in cells within spinal cord pain pathways may occur after a brief painful stimulus (Bullit, 1989; Fitzgerald, 1990; Hanley, 1988; Hunt, Pini, & Evan, 1987) and may lead to the development of chronic pain. More severe pain may also be more difficult to control and lead to increased

lengths of hospitalizations, immediate recurrence, and increased frequency of hospitalizations. This scenario could eventually impact the child's quality of life (Fuggle, Shand, Gill, & Davies, 1996), school attendance, performance and achievement, (Eaton, Haye, Armstrong, Pegelow, & Thomas, 1995; Shapiro et al., 1995), activity and function (Shapiro, Dinges, & Orne, 1990), and emotional adjustment (Barbarin, Whitten, & Bonds, 1994).

In order to minimize the severity of pain during painful episodes or possibly prevent propagation or immediate recurrence of painful episodes in children with sickle cell disease, changes in pain characteristics, functional status, and biomarkers of sickle cell disease, such as CBC values need to be monitored during the evolution of the painful episode. The identification of patterns to these changes may lead to the development of therapeutic approaches to prevent the propagation of pain or relapse. The effectiveness of various pain management strategies at different phases of the painful episode need to be evaluated so that changes may be made to obtain adequate pain relief.

SPECIFIC AIMS

The specific aims of this study, in a sample of children with sickle cell disease who are hospitalized with a painful episode, are:

1. To describe changes in three pain characteristics (i.e., intensity, location, quality) during the progression of a painful episode;
2. To describe changes in functional status (i.e., sleeping, eating, activity level) during the progression of a painful episode;
3. To describe changes in the presence or absence of selected signs and symptoms of vaso-occlusion during the progression of a painful episode;

4. To describe changes in CBC values (i.e., hemoglobin, hematocrit, white blood cell count, platelet count, reticulocyte count) during the progression of the painful episode;
5. To describe the relationship between changes in pain intensity and changes in pain location surface area during the progression of a painful episode;
6. To describe the relationship between changes in pain intensity and changes in the values of hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte count during the progression of a painful episode;
7. To describe changes in pharmacologic pain management strategies during the progression of a painful episode;
8. To describe the relationship between changes in children's self-reports of pain relief and changes in pharmacologic interventions during the progression of a painful episode; and
9. To describe the relationship between changes in three pain characteristics (i.e., intensity, location, quality) and pharmacologic interventions during the progression of a painful episode.

ASSUMPTIONS

1. The painful episode is managed at home for a variable number of days for each child prior to admission to the hospital. Therefore, the day of onset of a painful episode varies. The time of onset to the time of admission into the hospital and length of hospitalization also varies with each child.
2. Pain management strategies used to manage sickle cell pain will vary with each child at the point of entry into the hospital.

3. Children who are admitted for painful episodes of sickle cell disease are experiencing severe pain that may be at its peak, or may have been reduced by various attempts at pain management home or in the ED.
4. Children with sickle cell disease who are admitted to the hospital for reasons other than pain (e.g., fever, dehydration from vomiting and diarrhea, and acute chest syndrome) are at risk for experiencing pain.

DEFINITION OF TERMS

The following definition of terms were used in this study:

Children – male or female hospitalized patients, between the ages of 5 years and 19 years.

Sickle cell disease - a genetic disorder characterized by the presence of abnormal sickle hemoglobin (HgbS).

Pain intensity - a rating between 0 and 5 (for children 5 to 7 years) and between 0 and 100 (for children 8 to 19 years) that quantifies the severity of pain, as measured by the Oucher Pain Scale (Beyer & Knott, 1998); Appendix A.

Pain location surface area - the number of square units representing the surface area (height x width of the marked areas, measured by a standard transparent millimeter ruler), of the child's pain marked on the Body Outline Diagram of the Adolescent Pediatric Pain Tool (Savedra, et. al., 1990; Savedra, et., al., 1993; Appendix B).

Pain quality - the number and percent of sensory, evaluative, affective, and total words selected from the word list of the Adolescent Pediatric Pain Tool (Savedra, et. al., 1990; Savedra, et., al., 1993; Appendix B).

Progression - a consecutive sequence of days starting from day 1 of admission to the hospital to the day of discharge.

Painful episode - the occurrence of pain in the extremities, back, abdomen, chest, or head that lasted at least two hours, led to hospitalization, and could not be explained except by sickle cell disease (Platt et al., 1991).

Sleeping – a rating that quantifies the child's perception of the amount of sleep s/he had in the last 24 hours, using a 0-10 descriptive, numeric rating scale (Numeric Rating Scale for Sleeping, Appendix C).

Eating – a rating that quantifies the child's perception of the amount of oral intake s/he had in the last 24 hours, using a 0-10 descriptive, numeric rating scale (Numeric Rating Scale for Eating, Appendix C).

Activity Level – a rating that quantifies the child's perception of the amount of activity, s/he did in the last 24 hours, using a 0-10 descriptive, numeric rating scale (Numeric Rating Scale for Activity, Appendix C).

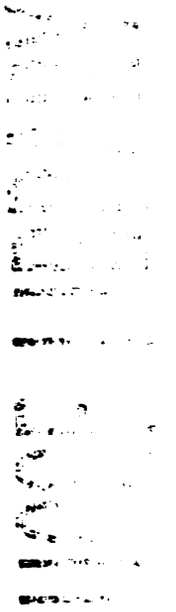
Signs and symptoms of vaso-occlusion – a number from 0 to 25 that quantifies the presence of twenty-five signs and symptoms, that were observed by the researcher, parent, or nurse during the previous 24 hours (Signs & Symptoms Checklist, Appendix D).

Complete Blood Count (CBC) values – values for hemoglobin, hematocrit, white blood cell count, platelet count, reticulocyte count as measured by laboratory standards, drawn once a day during hospitalization.

Pharmacologic pain management strategies – the amount, frequency, and route of

pharmacological agents administered to the child. A Medication Quantification Scale (MQS) score was calculated for each 24 hour period using a modification of the MQS developed by Steedman and colleagues (Steedman, Middaugh, Carson, Harden, & Miller, 1992, Appendix E).

Pain relief score - a rating that quantifies the child's perception of the amount of relief from the pain management strategies s/he is experiencing, using a 0-10 descriptive, numeric rating scale (Numeric Rating Scale for Pain Relief, Appendix C).



CHAPTER 2

LITERATURE REVIEW

A large body of research explains the pathophysiological mechanisms of sickle cell disease, from the molecular and cellular level to the mechanisms involved in its complications, such as acute chest syndrome, splenic sequestrations, and cerebrovascular manifestations. However, the pathophysiologic events that lead to the sensation of pain in sickle cell disease have not been studied directly. The activation of nociceptors after ischemic tissue injury and the consequent microinfarcts from vaso-occlusion of vessels related to sickling may explain the mechanisms of pain in sickle cell disease.

Few research studies focused on detailed explanations of the painful episodes during vaso-occlusive events. Yet, pain during vaso-occlusive events is the most common clinical manifestation and the most frequent factor associated with emergency room visits and hospital admissions in children with sickle cell disease (Frush, Ware, & Kinney, 1995; Platt et al., 1991). Therefore, the primary aim of this research is to describe the pain experience, pain management, and pain outcomes in hospitalized children during vaso-occlusive events. This review will first describe pain mechanisms in sickle cell disease and introduce the UCSF Symptom Management Model which is the conceptual framework for this study. Then, research findings related to pain experience, pain management, and pain outcomes will be reviewed and critiqued as they relate to the context of this study.

Pain Mechanisms in Sickle Cell Disease

Pain occurs at any location that contains nociceptors. Nociceptors are primary afferent nerves with peripheral terminals that respond differently to tissue damaging

stimuli (Ballas, 1998a; Ballas, 1994). It may be localized, involve several areas, be diffuse, or be migratory. Pains are generally bilateral and symmetrical and may move from one joint to another. Tenderness or pressure over affected sites is common. Pain affecting the sternum or ribs may be pleuritic in nature; lungs may be normal and there is often acute, localized tenderness with swelling of the affected rib (Serjeant, 1992). Pain perceived as constant, gnawing, aching, sharp, or throbbing possibly results from the activation of nociceptors in the cutaneous, subcutaneous, and deep tissues (Fields, 1987; Payne, 1967; Wall, 1994). It may be well localized and may involve the musculoskeletal system. Serjeant and colleauges (1992) reported that pain occurred most frequently in the lumbar spine (49%), abdomen (32%), femoral shaft (30%), and knees (21%) in 118 patients. Abdominal pain was significantly associated with distention and/or ileus (31%).

Pain perceived as constant, dull, deep, or squeezing, and which may be accompanied with nausea, vomitting, hypertension, tachycardia, tachypnea, and diaphoresis may result from the activation of nociceptors in the gastrointestinal tract, cardiopulmonary system, or genitourinary tract (Fields, 1987; Payne, 1967; Wall, 1994). It may result from activation of nociceptors by irritation, torsion, traction, contraction, impaction, stretching or distention of the thoracic and abdominal viscera. It may not be well-localized. Patients with acute chest syndrome, splenic sequestration, and hepatic crisis may experience this type of pain (Ballas, 1994). Pain perceived as severe, constant, dull ache, with superimposed paroxysms of burning, shooting, or electric shock-like sensations may result from ischemia, necrosis, inflammation, or infarction to the central and/or peripheral nervous tissues (Ballas, 1994).

The series of biochemical, neurological, and electrochemical events which stimulates the nociceptors as a result of tissue ischemia and infarction is collectively referred to as nociception (Fields, 1987; Katz & Ferrante, 1993). Four pathophysiologic mechanisms are involved in this process: 1) transduction, 2) transmission, 3) modulation, and 4) perception.

Transduction

During transduction, the chemical mediators that activate and sensitize nociceptors in ischemic events are converted to an electrical impulse in the primary afferents. The impulse frequency makes it accessible to the brain for decoding and interpreting the message as a painful experience.

The pain in sickle cell crisis begins with tissue ischemia and the release of inflammatory mediators, such as bradykinin, histamine, eicosanoids, prostaglandins, cytokines, substance P, and α1-acid glycoprotein (Bonica, 1977; Hargreaves & Dionne, 1991). These chemical mediators activate and sensitize nociceptors, which produce pain and itching in some patients (Bonica, 1977; Hargreaves & Dionne, 1991). In addition to inflammatory mediators, endogenous pyrogens, such as interleukin-1 (IL-1) activates the cyclooxygenase gene and lead to the synthesis of prostaglandins E_2 and I_2.

Prostaglandins, leukotrienes, nerve growth factor, and bradykinin sensitize peripheral nerve endings and facilitate the transmission of painful stimuli. Activated nociceptors release stored substance P in peripheral nerves and in the spinal cord, which further facilitates the transmission of painful stimuli. Bradykinin and substance P also cause vasodilation with extravasation of fluids that can lead to local swelling and tenderness (Ballas, 1998a; Cousins, 1989; Fields, 1987; Katz & Ferrante, 1993; Levin &

Taiwo, 1994). Serum levels of substance P (Michaels, Ohene-Frempong, Zhao, & Douglas, 1998), plasma levels of endothelin-1 and prostaglandin E_2 (Grado-Gonzales et al., 1998) were elevated in a sample of children with sickle cell disease and were highest in vaso-occlusive pain episodes.

The inflammatory response intitatied by ischemia and infarction enhances sympathetic activity and triggers the release of norepinephrine (Levin & Taiwo, 1994), which then causes more acute and severe pain (Ballas, 1998a). Endothelin-1 is a potent long acting mediator of vaso-constriction and inflammation which may play a key role in the cycle of ischemia and inflammation that initiates and sustains pain during vaso-occlusive episodes (Grado-Gonzales et al., 1998).

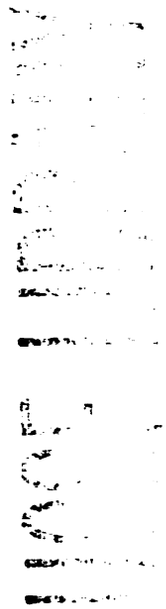
Transmission

During transmission, the electrical impulses carrying the coded information about the painful stimuli are relayed to and through the central nervous system, to brain regions where pain sensation is perceived. Pain stimuli generated by activation of nociceptors are conducted along the A-δ and C fibers within the peripheral nerves. The A-δ fibers are thin myelinated fibers, which carry sharp, localized pain sensation at a conduction velocity of nearly 20 m/sec. The C fibers are unmyelinated and carry dull, diffuse pain sensation at a slow rate of less than 2 m/sec. These fibers transmit pain into the dorsal horn of the spinal cord.

The dorsal horn of the spinal cord is a complex structure consisting of six laminae or layers, with lamina I being the most dorsal. Cells in laminae I, IV, and VI respond to noxious stimuli. Most of the sensory processing and pain modulation occurs in lamina II and III, the substantia gelatinosa of the dorsal horn (Fields, 1987; Melzack & Wall, 1965;

Wall, 1994). This location is where nociceptive and nonnocicieptve input are integrated in the spinal cord. The dorsal horn recieves pain stimuli from the A-δ and C fibers via the dorsal root ganglion (Melzack & Wall, 1965; Wall, 1994).

Spinal column transmission cells mediate the transfer of information from the substantia gelatinosa to the brain via dorsal column fibers (Melzack & Wall, 1965). The spinothalamic tracts carry sensory information from the spinal cord to the brain. The ascending spinothalamic tract is divided into two anatomically and physiologically distinct subsystems, the neospinothalamic and paleospinothalamic tracts. The neospinothalamic tract projects to the ventro-lateral and posterior thalamus, where it synapses into fibers that project to the somatosensory cortex of the parietal lobe. This tract conveys the sensory-discriminative aspects of pain. The paleospinothalamic tract projects to the reticular formation, the pons, limbic midbrain area, and to the medial thalamic nuclei. These fibers connect with fibers in the hypothalamus and limbic forebrain structures which have diffuse projections to many different parts of the brain (Fields, 1987; Wall, 1994).



Modulation

During modulation, several neural mechanisms modify the transmission of the nociceptive stimuli, which may inhibit or enhance the transmission of pain. A gating mechanism in the spinal cord controls the transmission of nerve impulses from afferent fibers (Melzack & Wall, 1965). The closing and opening of the gate is determined by the relative amount of activity in small (A-δ and C) and large (Aβ) afferent fibers. When the activity of the large fibers is greater than the activity of the small fibers, the gate closes and inhibits the transmission of afferent pain impulses. On the other hand, when the

small fibers exhibit more predominant acitivity, the gate opens and facilitates the transmission of pain impulses.

There are supraspinal descending neural systems that also modulate the transmission of pain in the dorsal horn (Basbaum, 1983; Basbaum & Fields, 1984). The periaqueductal gray matter (see figure) of the midbrain sends information to the nucleus raphe magnus. Long fibers descend from the periaqueductal gray matter via the dorsolateral funiculus and terminate in laminae I, II, and V of the dorsal horn for modulation of afferent nociceptive impulses.

Perception

During perception, the transduction, transmission, and modulation of nociceptive information are developed into the subjective, sensory, and emotional experience of pain. The role of the cerebral cortex in pain perception is just beginning to be researched. Some reports indicate that large lesions of the somatosensory cortex do not alter pain. Others state that small cortical lesions ablate pain perception. Recent functional imaging studies have implicated that the somatosensory and limbic system-related neocortex is involved in human pain perception (Casey, Minoshima, Berger, & Koeppe, 1994).

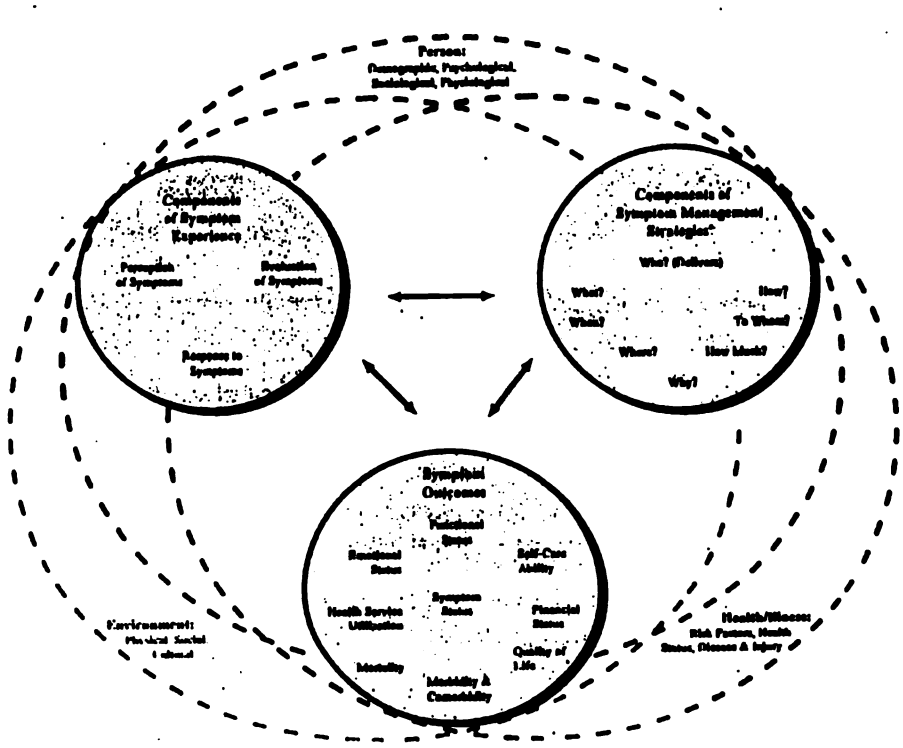
The UCSF Symptom Management Model

The UCSF Symptom Management Model was designed by the Symptom Management Faculty Group at the University of California San Francisco, School of Nursing to promote a comprehensive approach to symptom management (Larson et al., 1994). It was developed as a guide to their study of symptoms across different illnesses and ages. The aim of the model is to facilitate communication and a sharing of research

questions, instruments to measure common variables, and research findings related to symptom management (Carrier-Kohlman, 1992).

In the faculty group's early investigations of symptoms (pain, fatigue, dyspnea) questions about the symptom experience, about characteristics of the symptom itself, or about the meaning of the symptom were asked. These investigations were then followed with correlational studies examining the correlates of the symptom that were hypothesized to increase or decrease the symptom, or make the symptom go away all together. These concepts or categories of variables became the Symptom Experience, the first dimension in the model and included the perception of the symptom, variables that affect the perception of the symptom, characteristics of the symptom, and response to the symptom or a cluster of symptoms.

The UCSF Symptom Management Model views symptoms as subjective experiences. Because symptoms are subjective, it is assumed that symptoms are difficult to evaluate. The symptoms reflect changes in a person's physiological and psychosocial function, sensation, or cognition. The symptoms cause distress in the person. It is symptom distress that causes the patient to seek medical help (Grant, 1992). The model has three interrelated dimensions (see diagram): symptom experience, symptom management, and symptom outcomes.



Reprinted from: Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E. S., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S., & Taylor, D. (2001). Advancing the science of symptom management. Journal of Advanced Nursing, 33(5), 668-676. Larson, P. J., Carrieri-Kohlman, V., Dodd, M., Douglas, M., Faucett, J., Froelicher, E., Gortner, S., Janson, S., Lee, K., Miaskowski, C., Savedra, M., Stotts, N., Taylor, D., & Underwood, P. (1994). A Model for Symptom Management. IMAGE: Journal of Nursing Scholarship, 26(4), 272-276.

Symptom Experience

The symptom experience involves the interaction of three elements: perception of a symptom, evaluation of a symptom, and response to a symptom. Perception of a symptom occurs when an individual notices a change from the way he or she usually feels or behaves. Perception is gathered by the senses and is a conscious cognitive interpretation of a symptom. The evaluation of a symptom occurs when an individual characterizes the symptom. Some characteristics include the intensity, location, temporal nature, frequency, and the associated pattern of disability. Other characteristics may be the danger, the disabling effect, or whatever evaluated threat is posed by a symptom.

Response to a symptom occurs when the individual shows physiological, psychological, and behavioral changes in response to the symptom. Physiological responses include heart palpitations, changes in respiratory rate, menstrual cycle events, fragmented sleep, and other physical manifestations of the symptom. Psychological responses include mood changes, decreased ability to concentrate, altered self-esteem, and other cognitive or affective changes. Behavioral responses include verbal or social communication (crying, yelling), conflicts, alterations in personal function (social withdrawal, change in sleep patterns), or change in role performance (Larson et al., 1994).

Symptom Management

The model assumes that all symptoms need to be managed. It assumes that symptom management strategies influence or control both the symptom experience and the symptom outcomes. The goal of symptom management is to prevent or minimize negative outcomes. Biomedical, professional, and self-care strategies may be used. Interventions can be aimed at one or more of the components in the symptom experience and can influence one or more desired outcomes. It is a dynamic process and may require changes over time in response to a patient's acceptance or lack of acceptance of the strategy. The patient and family forms a partnership with the health care providers in an effort to prevent or manage the symptom. Medications as well as other interventions to control or decrease the symptoms are considered to fit within the context of the situation (Larson et al., 1994).

Symptom Outcomes

Ten multidimensional indicators are related to symptom outcomes and are associated with the symptom experience and its management. These are: symptom

status, self-care ability, financial status, morbidity, comorbidity, mortality, quality of life, health service utilization, emotional status, and functional status.

Surrounding the three dimension circles in the model are three larger interrelated domain circles (see Appendix 2): person, environment, and health/illness. These represent the variables that may affect symptom experience, symptom management, and symptom outcomes. The larger circle representing person variables includes the demographic (age, sex, ethnicity, marital status, financial status), psychological (personality traits, cognitive capacity, motivation), social (family unit, culture, religion), and physiological variables (rest and activity patterns, physical capacity). The second large circle represents environmental variables. The environment represents the conditions, the circumstances, the atmosphere and the background within which a symptom is perceived. It includes the physical environment (home, work, play), the social environment (family, social support network), and cultural environment (beliefs, values, and practices). The third large circle represents the health/illness variables, which includes risk factors, health status, and disease or injury.

Pain Experience

The small number of research studies that describe the pain experience of children with sickle cell disease primarily focused on pain intensity (Conner-Warren, 1996; Shapiro et al., 1990; Shapiro et al., 1995; Sporrer, Jackson, Agner, Laver, & Abboud, 1994; Walco & Dampier, 1990). Only one study reported on the relationship between pain intensity and the number of painful body locations (Sporrer et al., 1994). In addition, only one study assessed the sensory, evaluative, and affective qualities of vaso-occlusive pain (Walco & Dampier, 1990). No studies were found that describe changes

in these three pain characteristics during the progression of a painful episode. Longitudinal designs were used frequently. However, techniques for analyzing longitudinal data were not utilized. Participants were primarily recruited from outpatient settings, either from clinics or from home. None were recruited from emergency departments or from day hospitals, and only a few were recruited from acute care hospital settings.

Pain Intensity

Pain intensity was measured most frequently using the 100 mm or 10 cm Visual Analog Scale (VAS) (Shapiro et al., 1990; Shapiro et al., 1995; Walco & Dampier, 1990). Two faces scales, the Oucher Pain Scale (Beyer & Aradine, 1986; Beyer & Aradine, 1988; Beyer, Denyes, & Villarruel, 1992; Beyer & Knott, 1998) and the Wong-Baker Faces Pain Scale (Wong & Baker, 1988), were used in two studies (Conner-Warren, 1996) and (Sporrer et al., 1994, respectively). Table 1 summarizes the sample size, gender, mean age, age range, the instruments used, mean pain intensity scores, and various sources of pain intensity ratings in these studies.

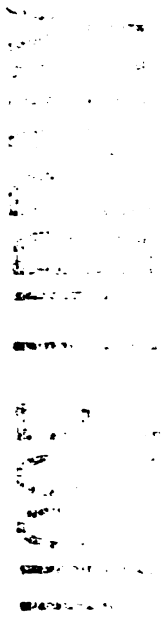


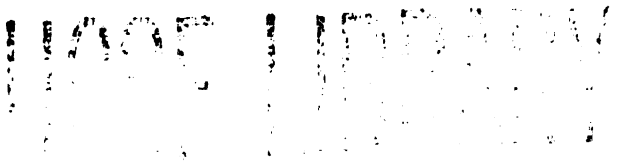
Table 1
Mean pain intensity scores of children with sickle cell disease during painful episodes.

Author, Year	Sample size Gender Mean age age range	Instruments Used	Mean Pain Scores	Sources of Ratings
Conner-Warren, 1996	N=30 15 F; 15M 11.23±3.4yo 4 to 18 yo	Oucher Scale 0=no hurt to 5=biggest hurt	2.3 ± 1.3	Painful episodes at home
Shapiro, et al, 1990	N=15 11.3 yo 6 to 16 yo	100mm VAS 0=none to 100=worst	35 ± 12	VOE pain rating at home In the morning
		100mm VAS 0=none to 100=worst	43 ± 22	VOE pain rating at home In the evening
		100mm VAS 0=none to 100=worst	13 ± 20	"other noncrisis" pain rating on VOE pain days
		100mm VAS 0=none to 100=worst	36 ± 24	"other noncrisis" pain ratings on pain-free days
Shapiro, et al, 1995	N=18 7F; 11M 12.9 ± 2.5 yo 8 to 17 yo	100mm VAS 0=none to 100=worst	29	Painful episodes at home

Sporrer, et al, 1994	N=9 1F; 8M 7.3 yo 3 to 12yo	Wong-Baker Faces Pain Scale 0=no hurt to 5=biggest hurt	2.1 ± .983	Pain in younger children (3 to 12 yo) before pain management Protocol in the hospital
	N=8 4F; 4M 15.5 13 to 18yo	Wong-Baker Faces Pain Scale 0=no hurt to 5=biggest hurt	3.7 ± .727	Pain in older children (13 to 18 yo) before pain management Protocol in the hospital
	N=6 2F; 4M 3 to 17yo	Wong-Baker Faces Pain Scale 0=no hurt to 5=biggest hurt	2.67	Extremity pain (arms, legs, long bones)
	N=4 0F; 4M 5 to 18 yo	Wong-Baker Faces Pain Scale	2.85	Abdomen, chest, back pain
	N=7 2F; 5M 4 to 18 yo	Wong-Baker Faces Pain Scale 0=no hurt to 5=biggest hurt	2.96	Diffuse pain
Walco & Dampier, 1990	N=35 15F; 20M 11.1±3.22 yo 5 to 16 yo	10cm horizontal VAS 0=no pain to 10=severe pain	1.51 ± 3.00	Child/adolescent's rating of present pain
		10cm horizontal VAS 0=no pain to 10=severe pain	2.0 ± 3.80	Parent's rating of child's present pain
		10cm horizontal VAS 0=no pain to 10=severe pain	1.12 ± 1.93	Physician's rating of child's present pain
		10cm horizontal VAS		Child/adolescent's rating of worst pain

0=no pain to 10=severe pain	3.76 ± 4.03	in the past week
10cm horizontal VAS 0=no pain to 10=severe pain	3.89 ± 1.99	Parent's rating of child's worst pain
10cm horizontal VAS 0=no pain to 10=severe pain	8.79 ± 1.99	Child/adolescent's rating of worst pain managed at home
10cm horizontal VAS 0=no pain to 10=severe pain	8.94 ± 2.75	Parent's rating of child's Worst pain managed at home
10cm horizontal VAS 0=no pain to 10=severe pain	7.70 ± 3.27	Child/adolescent's rating of Worst pain managed in hospital
10cm horizontal VAS 0=no pain to 10=severe pain	8.94 ± 2.75	Parent's rating of child's Worst pain managed in hospital
10cm horizontal VAS 0=no pain to 10=severe pain	3.47 ± 3.69	Adolescent's rating of average pain
10cm horizontal VAS 0=no pain to 10=severe pain	1.84 ± 2.92	Parent's rating of average pain

VAS = Visual Analog Scale; VOE = Vaso-Occlusive Event



Differences in pain intensity ratings were compared between: 1) morning versus evening (Shapiro et al., 1990); 2) vaso-occlusive pain versus non-vaso-occlusive pain (Shapiro et al., 1990); 3) male versus female participants (Conner-Warren, 1996); 4) younger versus older children (Sporrer et al., 1994); children versus parents and physicians (Walco & Dampier, 1990); 5) pain managed at home versus pain managed in the hospital; and 6) pain management before, during, and after pharmacologic interventions (Christensen, et., al., 1996; Dampier, et. al., 1995; Grisham & Vichinsky, 1996; Jacobson, et. al., 1997; Robieux, et. al., 1992; Shapiro, et. al., 1993; Trentadue, et. al., 1998; Yaster, et. al., 1994). Daily changes in pain intensity ratings during the progression of the episode, from the time of onset to the time of resolution, or from the time of admission to the hospital to the time of discharge were not examined.

Pain Intensity During Hospitalization. Sporrer and colleagues (1994) characterized pain reporting among children (3 to18 years, n=17) who were admitted to the hospital for painful episodes. Pain intensity scores using the Wong-Baker Faces Pain Scale (Wong & Baker, 1988) were collected at one and two hours after analgesic administration and then every 4 hours with vital signs while the patients were awake. Pain intensity scores were also obtained at one and two hours after dosing adjustments. Only the first ten scores were used in the analysis because the earliest days of hospitalization were expected to yield comparable pain reports among all patients, regardless of length of stay. This analysis represented only the first 24 to 36 hours of hospitalization.

The analysis primarily compared differences among mean pain scores and the range of pain scores (see Table 1) as reported by children grouped by age, pain location, and length of hospitalization (less than or equal to four days versus longer than four days). Changes in pain intensity scores during the progression of the painful episode in the hospital were not reported. The relationship between pain intensity scores and pain management strategies were also not reported.

Differences in pain scores were compared with children whose pain occurred in three pain location groupings (Group I - extremity pain only, Group II – pain in abdomen, chest, neck, and Group III – diffuse pain). Seventeen patients were grouped according to pain location: six patients in Group I (extremity pain only), four in Group II (abdominal, back, or chest pain only), and seven in Group III (diffuse pain). No significant differences were found in mean pain scores by location. The mean pain scores were 2.67, 2.85, 2.96 for Groups I, II, III, respectively. The number of painful sites was not correlated to the level of pain intensity; that is, r=.00, p>.05 for VAS scores and r=.12, p>.05 for categorical ratings (Walco & Dampier, 1990). The mean lengths of hospital stay were longer for patients with diffuse pain (11.7 days) than for patients with pain localized to extremity (5.0 days) or abdomen, back, and chest (6.3 days) (Sporrer, 1994). The relationship between pain intensity scores and pain location surface areas were not examined.

Walco and Dampier (1990) examined the pain experience of hospitalized patients with sickle cell disease (12 to 25 years, n=12) whose primary diagnosis was vaso-occlusive pain. Lengths of hospitalizations ranged from two to nine days. Patients were asked once a day (between 9:00 am and 12:00 noon), by the attending physician or nurse

clinician about their current levels of pain. Two pain intensity measures were used: a categorical pain scale (0=no pain, 1=mild pain, 2=uncomfortable pain, 3=distressing pain, 4=horrible pain, 5=excruciating pain) and a 10 cm visual analog scale (VAS). Data from medical records were also gathered including type of current medication, dosage, route of administration, and time since the last dose was administered.

The relationships among the two self-report measures of pain intensity and between the pain intensity and analgesic dosage were examined. High correlations were found between the ratings on the categorical pain scale and the VAS ($r=.84$, $p<.001$). Small but statistically significant correlations were found between analgesic dosages and the ratings on the categorical pain scale ($r=.33$, $p<.01$), and between analgesic dosages and the VAS scores ($r=.24$, $p<.05$). The analgesic dosages reflected opioids (morphine, meperidine, and hydromorphone) only. The overall effectiveness of other pharmacologic agents (ketorolac, ibuprofen, acetaminophen with codeine, diphenhydramine, lorazepam) and their combinations with opioids for pain management were not reported. The relationship between analgesic dosages and pain relief scores were not examined.

Trends in mean daily pain intensity ratings were examined over the two to nine day stay in the hospital. There was a decrease in pain intensity scores with both the categorical pain scale and the VAS over the course of days in the hospital. Pain intensity ratings during hospital days 1 to 3 were significantly higher than during days 4 to 6, or days 7 to 9. However, this trend represents changes in mean ratings grouped by hospital day, and may not reflect patterns of change in pain intensity ratings among individuals during the progression of the painful episode in the hospital.

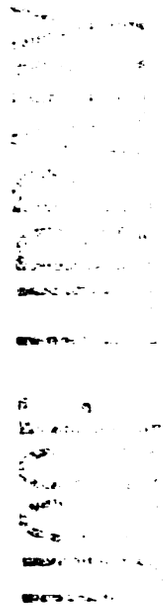
Mean pain intensity ratings during hospital days 1 to 3, were also higher than mean pain intensity ratings for present pain ($t = 6.01$, $p<.01$) reported by children (age 5.4 to 15.9 years, n=35) who were asked during a regularly scheduled appointment in the sickle cell clinic about their present pain, worst pain in the past week, average pain (12 years and older), worst pain experienced at home, and worst pain experienced in the hospital (Walco & Dampier, 1990). While mean pain intensity ratings during hospital days 1 to 3 were not significantly different from either worst pain managed at home ($t=1.76$, $p>.05$) or worst pain managed in the hospital ($t =.44$, $p>.05$) the changes in worst pain intensity ratings during each day of hospitalization were not reported during the evolution of the painful episode in the hospital.

Pain Location

Only two research studies (Sporrer et al., 1994; Walco & Dampier, 1990) explored pain location in children with sickle cell disease. Children (3 to18 years, n=17) who were admitted to the hospital for painful episodes were grouped according to pain location: Group I - extremity pain only (n=6); Group II – pain in abdomen, chest, and/or back only (n=4); and Group III – diffuse pain (n=7) (Sporrer et al., 1994). Body outline diagrams were not used to mark precise areas of pain location. The means of the first ten pain intensity scores recorded during the first 24 to 36 hours of hospitalization and lengths of hospitalization were compared among the three groups. The mean pain scores were not statistically different (see Table 1). However, this finding may be due to the small sample size in each group. The mean length of stay for group III (11.7 days) who had diffuse pain, was significantly longer ($p<.05$) than for either group I who had only extremity pain (5.0 days) or group II who had only abdominal, chest, or back pain (6.3

days). When six patients with complications were eliminated from the analysis, the difference in length of stay between Group I (5.0 days) and Group III (8.5 days) was significant. While differences in pain intensity ratings among various locations were compared, the effect of pharmacologic interventions on pain location was not examined.

Walco and Dampier (1990) asked children (age 5.4 to 15.9 years, n=18) during a regularly scheduled appointment in the sickle cell clinic to use a body diagram to specify pain locations and use four colors to represent various levels of pain intensity. Results showed that children were able to use colors to represent various levels of pain intensity in different parts of the body, with red and green being the most frequently chosen colors to represent severe pain. No additional analysis related to the body diagram was reported.



No study was found that used body outline diagrams (BOD) in children with sickle cell disease who were hospitalized for painful episodes. No study was found that examined the possibility that there may be changes in pain location as measured by surface area (height x width in millimeters of marked areas on the BOD's), number of marked areas on the body outline diagram, or the overall spatial distribution of pain in different locations in the body as the painful episode evolved. Furthermore, no study was found that examined changes in pain location surface area in relationship to pharmacological interventions.

Pain Quality

The sensory, evaluative, and affective qualities of pain in children with sickle cell disease were explored in only one research study. Walco and Dampier (1990) asked children (age 5.4 to 15.9 years, n=18) during a regularly scheduled appointment in the

sickle cell clinic to select from a list of 46 pain descriptors those words that represented their pain experiences. The words were ordered to intersperse the three qualities of pain. The designation of the type of descriptor was based on previous research by Melzack and colleauges (1975; 1971). The vaso-occlusive pain was most frequently described as "aching". Word choices were presented in a table showing the percentages of most frequently chosen pain descriptors and mean totals by category among parents, adolescent (12 years and older), and children (5 to 11 years).

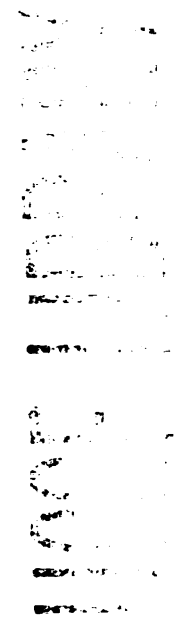
No study was found that examined the sensory, affective, and evaluative qualities of pain in hospitalized children with sickle cell disease. In addition, no study was found that examined changes in pain quality as the painful episode evolved, or in relationship to pharmacologic interventions.

Pain Management

The small number of studies related to pharmacological interventions used for pain management in children with sickle cell disease were predominantly descriptive and utilized a repeated measures design (i.e., before, during, and after medications) or a prospective time series design with repeated measures.

Two studies were retrospective chart reviews (Shapiro, Cohen, & Howe, 1993; Yaster, Tobin, Billett, et al., 1994) and one was a randomly assigned, double blind clinical trial (Griffin, McIntire, & Buchanan, 1994). No study was found that utilized a longitudinal design to examine changes in pharmacological interventions and their relationship with children's self-report of pain relief or to examine changes in pain intensity or pain location surface area throughout the course of hospitalization.

Four research studies on pharmacologic management were descriptive. One study described the pharmacokinetics of intravenously administered morphine during steady state (Robieux, Kellner, Coppes, Good, O'Brodovich, Manson, Olivieri, & Koren (1992) and another study described morphine use during painful episodes (Dampier, Setty, Logan, et al, 1995). One study described the dose ranges, utilization patterns, and frequency and types of problems encountered with the use of patient controlled analgesia (Shapiro, Cohen, & Howe, 1993). The dose-concentration relationship and clinical effects of transdermal fentanyl (Christensen, Wang, Harris, et al, 1996), and continuous epidural fentanyl in children who were unresponsive to conventional analgesic therapy (Yaster, Tobin, Billett, et al, 1994) were also described. Table 2 provides a summary of findings from these studies. While these studies examined the safety (i.e., side effects and complications), costs (i.e., length of hospital stay, amount of opioid use, number of days on PCA) and the effects of opioids on pain intensity), no studies described the effects of these pharmacological agents on the child's perception of pain relief, pain location, pain quality, and functional status (eating and activity).



Three studies compared the efficacy and safety of medications in different delivery modes: continuous infusion of morphine versus intermittent parenteral opiates (Robieux, Kellner, Coppes, et al, 1992); intravenous ketorolac versus intravenous meperidine (Grisham & Vichinsky, 1996); and high dose PCA (patient controlled analgesia) with a low basal infusion rate versus low dose PCA with a high basal infusion rate (Trentadue, Kachoyeanos, & Lea, 1998). Two studies examined the effectiveness of non-analgesic adjunctive therapies: 50% oxygen administration with a continuous infusion of morphine (Robieux, Kellner, Coppes, et al, 1992) and high dose intravenous

methylprednisolone (Griffin, McIntire, & Buchanan, 1994). Table 2 provides a summary of findings from these studies.

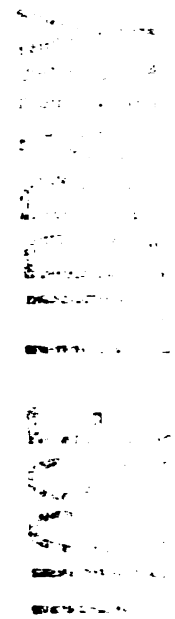
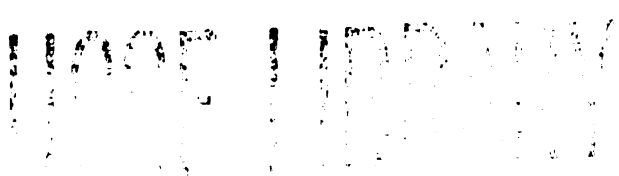


Table 2

Effectiveness of Pain Management Strategies

Author, Year	Pain Management Strategies	Sample Size Gender Mean Age Age Range Setting Design	Outcome Measures	Effectiveness of Pain Management Strategies
Christensen, et al, 1996	**Transdermal fentanyl** Applied to chest wall, back, or upper arm Changed q 48 hrs, delivered at 25 µg/hr to max of 75 µg/hr Decreased if clinical response or signs of toxicity occurred Supplemental: .02mg/kg PCA with 6 min lockout interval; .25mg/kg max q 4hr	N=10 9 to 16 yo 3 M/7F LeBonheur Children's Medical Center, Memphis, Tennessee Descriptive Design	RR, BP Oxygen sats q 2 hrs verbal pain scores (0 = no pain to 9 = worst pain scale) sedation rating scores: 1= wide awake, 2=drowsy, 3=dozing intermittently, 4 = mostly sleeping, and 5=awakens only when aroused fentanyl dose morphine requirement	No significant difference in the pain rating or the amount of supplemental morphine required during four 12 hr intervals. The total amount of narcotic analgesic used during two 24 hour time periods with use of transdermal fentanyl was greater than that used prior to study entry. Patients had a delay of at least 24 hrs before the fentanyl concentration reached the reported minimum effective concentration for adults. There was a continued drug accumulation beyond 24 hrs; the average fentanyl concentration was



.4ng/ml higher at 48 hr than at 24 hrs.

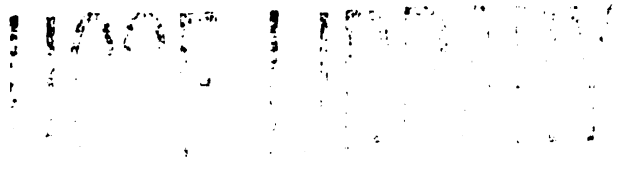
There was no significant change in the respiratory rate, blood pressure, or oxygen saturation during any of the time intervals

No report of skin irritation at site, but two patients reported poor adhesiveness.

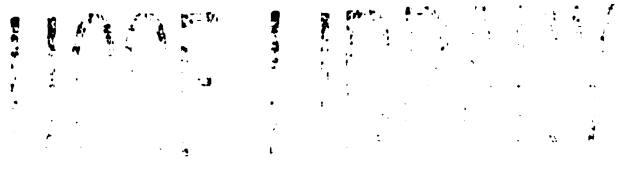
Sedation ratings were significantly higher during the 12 to 24 and 36 to 48 hr time periods, than with the 0 to 12 and 24 to 36 hr time periods, which primarily covered the time interval from 8 pm to 8 am.

Dampier, et al, 1995	**Continuous IV Morphine** .123 to .042 mg/kg/hr	N=18 mean age 14.7 yo, SD=4.3 yo 10 M/8F	Pain intensity by self-report on 0-10 categorical scale or a written questionnaire consisting of visual analog and categorical scales	Some patients continued to report severe pain despite adverse effects (excessive sedation, frequent emesis, or urinary retention) from high morphine levels.
	Single dose IV morphine .15 to .2 mg/kg over 30 seconds	mean age 16 yo, SD=4.9 yo 1 M/5F Marian Anderson Sickle Cell Center, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania Descriptive Design		Decrease in pain intensity peaked at 20 to 30 minutes, which represented only a 10% to 20% reduction from the initial pain intensity value.

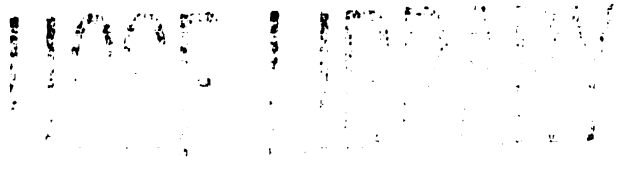
Griffin, et al, 1994	**Morphine + Methylprednisolone** 2 doses of saline placebo or methylprednisolone at 15mg/kg IV over 30 minutes, 24hr apart each dose, + morphine .1mg/kg IV q 2hrs prn moderate to severe pain, may be increased to .15mg/kg x8 over a 24 hr period, or started continuous IV morphine at the discretion of physician	N=56 17 M/13F N=30 16 M/10F received placebo N= 26 received methylprednisolone 2-19 yo mean 7.7 yo Children's Medical Center of Dallas Randomly assigned, double blind, placebo controlled	Number of IV morphine doses given need for continuous morphine duration of IV and PO analgesia clinical complications such as acute chest syndrome toxic reactions to steroids (headache, psychological disturbances, hypertension, cardiac dysrhythmia, infections complications)	The age adjusted duration of inpatient analgesic therapy was significantly longer for patients who received placebo than for those who received methylprednisolone. No significant difference was noted between the groups in the incidence of acute chest syndrome. The patients who received methylprednisolone required, on average, fewer morphine injections than those who received placebo, and received less morphine, but this difference was not statistically significant. No complications related to corticosteroid use (such as hypertension, gastrointestinal bleeding, or unusual alterations in behavior) were observed during the study.



Grisham & Vichinsky, 1996	**Meperidine vs. Ketorolac** IV meperidine at 1.5mg/kg or ketorolac at l mg/kg; after 2.5 hours, those with complete relief went home; those with persistent pain received the alternate drug of either meperidine or ketorolac	N=20 n=10 Ketorolac n=10 Meperidine 11 to 19 yo 55% M 45% F ER, Children's Hospital Oakland, Oakland, California Blinded crossover clinical trial	<u>Sedation scale</u> 0 = wide awake, 1=drowsy, but not sleeping, 2=sleeping intermittently, 3 = sleeping constantly, awakes with verbal stimulation, 4=sleeping constantly, arouses to tactile stimulation and stays awake >1 minute, 5=sleeping constantly, arouses to tactile stimulation and stays awake < 1 minute, 6=sleeping constantly, unarousable; recorded q 30 minutes for 150 minutes, and for additional 150 minutes if second analgesic received pain scores using a visual analog scale (vertical ruler marked from 0 no pain to 80 worst pain) categorical scale (no pain, slight pain, mild pain, moderate pain, strong pain)	Patients who received ketorolac had significantly larger decreases in the VAS pain ratings, than those who received the meperidine, over the 150 minutes. The greatest decrease in pain scores occurred during the first 30 minutes for both drugs, with the mean VAS score 39 after ketorolac and 54 after meperidine, which represents a greater amount of pain relief after ketorolac compared with meperidine. Patients who received ketorolac continued to show a decrease in VAS scores with a mean of 33 at 120 minutes; patients who received meperidine showed a small but persistent increase in the VAS, with a mean of 57 at 120 minutes. Ketorolac patients were still reporting significantly less pain than meperidine patients, with VAS scores of 36 versus 56. There was no significant difference between the mean VAS scores of either group at 150 minutes, with a mean VAS of 38 in the ketorolac/meperidine group, and 51 in the meperidine/ketorolac group.



Jacobson, et al, 1997	**Oral Morphine vs. Intravenous Morphine** loading dose of IV morphine (.15mg/kg) followed by randomly assigned PO morphine (1.9mg/kg q 12 hrs) + IV saline placebo vs. IV morphine .04mg/kg + placebo tablet (n=26)	N=50 28 M/22F mean age 11.2 years IV group (n=26), PO group (n=24) ER, Hospital for Sick Children, Toronto, Canada Double-blind, randomized, parallel-group design	Bieri Faces Pain Scale, Oucher Pain Scale, CHEOPS, and Clinical Pain Assessment (none, mild, moderate, severe, very severe) by a single investigator who was unaware of treatment group, assessed at 0900, 1300, 1700, and 2100 every day. Number of rescue analgesia in 24 hrs VS q 4 hrs, level of conscious q 4 on the Glasgow coma scale, oxygen saturation, end tidal carbon dioxide q 4 hrs Frequency and severity of other adverse events	Mean daily doses for oral is 2.99mg/kg, SD=.75 and for intravenous morphine is .81 mg/kg, SD=.30. Mean oral to parenteral dose ratio was 3.7. Overall rates of rescue analgesia did not differ significantly between the groups (.21, SD=.28 for IV; .33, SD=.36 for PO; p=.0591). Frequency of rescue analgesia by time of day was similar: .9 doses per day, SD=.7 for IV group; .7 doses/day, SD=.8 for PO group. Mean duration of pain requiring treatment with an opiate was 5.4 days, SD=2.6 in the IV group, 4.2 days, SD=1.7 in the PO group, p=.059. No significant differences between the PO and IV group in CHEOPS, Oucher, Faces, and Clinical Pain scales. Correlations between the scales (r=.5865 to .8980, p=.0001.



Robieux, et al, 1992	**Morphine + Oxygen Therapy** **<u>Phase A</u>** Control: analgesia ordered by physicians according to clinical judgment and prescription habits; 16 patients received oxygen at various concentrations and flow rates **<u>Phase B</u>** Protocol: MS loading dose of .15 mg/kg + 40 μg/kg/hr; may be increased q 8 hrs by 20 μg/kg/hr to a max of 100 μg/kg/hr; decreased by 20 μg/kg/hr q 8 hrs, when effective analgesia achieved and maintained for at least 24 hrs; decreased or stopped when serious side effects were observed; 11 randomized to receive air; 14 randomized to receive 50% oxygen, both via venturi mask	N=66 3-18 yo n=32 phase A n= 34 phase B Hospital for Sick Children, Toronto, Canada Prospective controlled, "before-and-after" evaluation of two analgesic regimen Randomized, double-blind, placebo-controlled of air vs. oxygen	Behavioral pain score q 8hrs, ranges from 0-10 VS q 2hrs pupil diameter and Glasgow Coma Score q 4 hrs presence of nausea, vomiting, sweating, and pruritus q 8hrs; episode of opiate toxicity (drowsiness or coma; pinpoint pupils, emesis, sweating or pruritus; respiratory rate <12/min	Duration of hospital stays were not different between groups in Phase A and Phase B. No difference in progression of crisis between groups in Phase A and Phase B, and for those patients receiving 50% oxygen versus room air. Duration of pain was similar in patients receiving 50% oxygen and patients receiving room air. Incidence of nausea, vomiting, pruritus, and sweating was not significantly different between the two groups. The fastest clearance rates were observed in children before puberty. The mean rate of infusion associated with two or more symptoms of opiate toxicity was 64 ± 30 μg/kg/hr. Mean steady state plasma concentration associated with symptoms of opiate toxicity was 107.4 nM ± 60 (range 36-190). Optimal rate of infusion, achieving effective analgesia without serious adverse effects, was 46 ± 26 μg/kg/hr (range 20-120).

Shapiro, et al, 1993	**PCA Morphine** Morphine for 39 patients Hydromorphone for 6 patients Nalbuphine for 1 patient	N=46 9 to 22 yo average age 15 years Retrospective Review of medical records Children's Hospital of Philadelphia	amount of drug actually delivered total dose allowed on day of maximum used	Average patient-controlled dose and hourly basal infusion were both 0.04 mg/kg; with lockout interval of 7 minutes. The average total hourly maximum dose allowed was .24 mg/kg and the maximum dose actually received on the day of heaviest use averaged .09 mg/kg. The number of times each patient triggered the device varied widely, especially on day of maximum use. Patients received 37% of the allowed dose on the day of maximum use (range 5-71% ± 17%). In 44% of uses, PCA parameters, such as the dose and basal infusion, were adjusted to increase analgesia or decrease side effects. For 70% of uses, oral opiates administered around the clock were substituted for the basal infusion once the pain began to improve and patients could take medications by mouth.

Trentadue, et. al., 1998	**High dose PCA (Patient Controlled Analgesia) + low basal rate versus Low dose PCA + high basal rate** **<u>Group I</u>** High PCA (0.25 mg/kg/dose) + low basal rate (.01 to .03 mg/kg/hr); 1 hour maximum limit at .1 to .15 mg/kg/hr **<u>Group II</u>** Low PCA dose (.01 to .02 mg/kg/dose) + high basal rate .05 to .2 mg/kg/hr); 1 hour; maximum .05 to .2 mg/kg/hr	N=26 children over 60 separate admission each admission recorded as separate entry N=30 patient admissions in each group 11M/15F mean age 15.16 yo range 11 to 18 yo Retrospective Review Children's Hospital at the Medical Center at Central Georgia	Length of hospital stay Actual number of days patients required the use of the PCA Cost of administering PCA as well as cost of narcotic Patient pain scores on a scale of 0 to 10, recorded q 4 hours HR, oxygen saturation, Total amount of morphine received group differences in total amount of morphine consumed total mg of morphine during hrs 1 to 24 and hrs 25 to 48 total number of days in the hospital,	<u>Group I</u> Used significantly less morphine during hospitalization, 6,681 mg total (M=222.71 mg), p=0.0112. Total morphine on hours 1 to 24 M=56.4267, p=.0657. Total morphine on hours 25 to 48 M=58.1367, p=0.368. Total morphine/hospitalization M=222.71, p=.0112, p=.0130 Total days PCA M=4.90, p=0.0012. Hospitalized fewer days M=5.033 days. Total cost of PCA $7,800. Cost of morphine syringes $5310. Discharged an average of 2.15 days sooner, with savings in nursing cost and hospital room charges. <u>Group II</u> Total morphine on hours 1 to 24 M=70.0267, p=.0657. Total morphine on hours 25 to 48 M=65.8667, p=0.368.

Oxygen saturation levels ranged from 86% to 100% without significant difference between the groups.

No significant difference in pain scores on day 1.

Highest reported pain score on day 2 of Group I (M=7.2222) is statistically different from group II (M=8.4286, p=0.0165.

Lowest reported pain score on day 2 is also statistically different
Group I (M=5.9630 and Group II M=7.4048).

No statistically significant differences in heart rate; highest ranged 66-124/min and lowest ranged 58 to 104/min on Day 1.

Yaster, et al, 1994	**Epidural Lidocaine + Fentanyl or Bupivacaine** 20G epidural catheters to lumbar or caudal epidural space for continuous infusion of lidocaine at 1.5mg/kg/hr; added fentanyl at .5 to 1.5μg/kg/hr for pain scores >5, or bupivacaine .2 to .4 mg/kg/hr	N=9 3 to 16 yo mean age 13 yo SD= 4 yo Retrospective Review of medical records	numerical verbal pain scale from 0 = no pain to 10 = worst pain Sa02 before and q 2hrs for 24hrs after insertion catheter related complications (inadvertent dural puncture, catheter migration, local and systemic infection, inability to place catheter correctly in the epidural space) anesthetic complications (seizures, cardiovascular collapse, respiratory depression, tachyphylaxis, elevated lidocaine plasma levels)	Analgesia was immediate and continuously effective in 9 of 11 crises. Pain scores decreased from 9 ± 1 to 1 ± 1 in 8 of 9 patients within 15 minutes of the insertion of the epidural catheter. Oxygen saturation increased from 91 ± 5% (range, 87 to 95%) to 99 ± 1% (ranged, 99 to 100%) after epidural analgesia. All patients were able to ambulate and none were sedated. One patient had severe lower extremity and back pain and was unable even to move in bed without major discomfort, the epidural abolished her pain, but it dislodged while moving furniture; after the epidural catheter came out, her pain returned, necessitating reinsertion of the catheter. Lidocaine toxicity did not occur; 5 patients developed tachyphylaxis to lidocaine within 24 to 72 hours after administration and required either the addition of fentanyl and /or substitution of bupivacaine for lidocaine. One patient became acutely hypotensive after bolus administration of local anesthetic.

While these research studies examined the safety and efficacy of medications administered singly, or compared safety and efficacy in different delivery modes, no studies were found that examined the changes in these medications and delivery modes as the painful episode evolved during the course of hospitalization.

Pain intensity was the most frequently used measure of effectiveness. Findings by Dampier and colleagues (1995) from a study of the pharmacokinetics of intravenously administered morphine in children with sickle cell disease indicated that patients (age 6 to 19 years, n=18) continued to report severe pain despite adverse effects (excessive sedation, frequent, emesis, or urinary retention) from high doses of morphine. In this study, the decrease in pain intensity (mean scores on VAS not reported) peaked at 20 to 30 minutes, which represented only a 10% to 20% reduction from the initial pain intensity value. Pain location surface area, the child's perception of pain relief, or increase in functional status may be other dimensions to utilize to assess the effectiveness of pain management strategies. However, these outcomes were not measured in any of the studies reviewed.

No studies were found that examined the overall effectiveness of medications (i.e., nonopioid, opioid, and adjuvant analgesics) that are used in combination to manage pain in sickle cell disease. Nonopioid analgesics that act at the level of peripheral nociceptors where pain impulses originate, are frequently prescribed for mild to moderate pain (Elander & Midence, 1996; Morrison & Vedro, 1989). Many inhibit the enzyme, cyclooxygenase, and decrease the synthesis of prostaglandin. They possess antipyretic, antiplatelet, and antiinflammatory properties, which decrease the inflammatory response and the perception of pain. They have minimal

neurologic side effects, no addictive potential, and no tolerance potential when used chronically (Amadio & Cummings, 1986; Beaver, 1988; Ferrer-Brechner & Ganz, 1984; Sunshine & Olson, 1994). Generally, nonopioid analgesics are useful in treating mild to moderate pain. Additive analgesic effects can be obtained when they are combined with opioids or adjuvant analgesics.

For those children who fail to respond to nonopioid analgesics, opioid analgesics should be used to provide pain relief (Foley, 1985). Opioids, such as codeine and oxycodone, are prescribed for children and are usually used orally for mild or moderate pain (Ballas, 1994). They are often used in combination with nonopioid analgesics, such as acetaminophen and aspirin (e.g., codeine and acetaminophen, hydrocodone and acetaminophen, oxycodone and acetaminophen , oxycodone and aspirin). The presence of acetaminophen and aspirin limits the amount of opioids that can be administered using these combinations (Foley, 1985; Jaffe & Martin, 1990; Twycross, 1994).

Even though in practice morphine is the most commonly used opioid in patients with sickle cell disease, meperidine is documented in the literature to be most frequently used (Davies, 1990; Pegelow, 1992). Meperidine is the least potent and shortest-acting of the synthetic opioids; it sometimes fails to provide analgesia for severe pain (Ford & Nahata, 1987); it was shown to be less effective for sickle cell disease pain than for postoperative pain (Abbuhl, Jacobson, Murphy, & Gibson, 1986); and it may increase the risk of seizures in patients with sickle cell disease because of the excitatory effects on the nervous system of its active metabolite, normeperidine (Liu, Gzesh, & Ballas, 1994; Pryle et al., 1992; Tang, Shimomura, &

Rotblatt, 1980). Morphine which is longer-acting is also commonly used (Brookoff & Polomano, 1992; Friedman, Webber, Osborn, & Schwartz, 1986) and was found to be more effective when compared with synthetic opioids (e.g., nalbuphine, butorphanol) that have mixed agonist and antagonist properties (Gonzales, Ornato, Ware, & D. Bull, 1988; Woods, Parson, & Strickland, 1990).

The pain in sickle cell disease is often accompanied by anxiety, psychomotor agitation, and insomnia. Adjuvant analgesics, such as antihistamines (e.g., hydroxyzine, diphenhydramine), tricyclic antidepressants (e.g., amitryptyline, imipramine), benzodiazepines (e.g., diazepam, lorazepam), antipsychotics (e.g., mellaril, haldol), barbiturates (e.g., phenobarbital), and anticonvulsants (e.g., phenytoin, carbamazepine, clonazepam), are beginning to be used in the treatment of sickle cell disease pain (Ballas, 1994). Adjuvants are medications administered in conjunction with a prescription drug to enhance the effect of the principal ingredient, and their primary indication is to treat symptoms (itching, anxiety, insomnia, depression) other than pain (Ballas, 1998b). Some of these drugs have analgesic properties independent of their psychological effects. Some exert their beneficial effects at the level of the reticular formation and the limbic system where the affective component of pain is believed to be mediated (Ballas, 1994). They reduce or counteract the adverse effects of opioid analgesics or treat psychological complications (1992; Foley, 1985; Hanks, 1984; Monks, 1994).

In the management of sickle cell pain, an adjuvant analgesic may be given at the initiation of treatment and before the side effects of the primary analgesic are manifest (Ballas, 1998c). An adjuvant analgesic may: increase the analgesic effect of

opioids; reduce the toxicity associated with the primary analgesic medication (e.g., nausea, pruritus); or improve other symptoms associated with sickle cell painful episodes, such as anxiety. No research studies were found that examined the effectiveness of combinations of nonopioids, opioids, and adjuvant analgesics in vaso-occlusive pain in children with sickle cell disease during the course of hospitalization. In addition, no studies were found that examined how these combinations change during the course of the hospitalization.

Pain Management Protocols

Sporrer and colleagues (1994) described a pain management protocol for patients with sickle cell disease that incorporated both opioids and nonopioids. According to the protocol, all patients initially received intraveous morphine sulfate (.15 mg/kg) every 3 hours with acetaminophen (10mg/kg) every 4 hours. If the pain intensity score, using the Wong-Baker Faces Pain Scale (Wong & Baker, 1988), was > 2, two hours after the initial administration, the dosing interval of morphine was changed to every two hours.

If pain scores persisted >2 after another two hours, ketorolac (30-60 mg IM loading dose, followed by 50% of the loading dose q 6 hours, for children >10 years who were receptive to IM dosing) or ibuprofen (20 mg/kg q 4 hour, for children <10 years or not willing to receive IM dosing). If pain persisted >2 for 24 hours, a continuous IV infusion of morphine was considered.

If pain was controlled at a score of ≤ 2 for a 24 hour period, patients were weaned from medication by first discontinuing ketorolac or ibuprofen, and then decreasing the dose of morphine by 25% every 12 hours. When pain scores remained

≤ 2 at 50% of the original intravenous morphine dose, patients were converted to oral medication (acetaminophen 300 mg with codeine 30 mg). If pain exacerbated during the weaning process, patients were placed on the previous dose of intravenous morphine for 12 hours and then the weaning process was restarted. Pain scores were obtained at least every 4 hours with vital signs, or at one and two hours after each dosing adjustment.

Two patients (n=17, 3 to 18 years) required a continuous infusion of morphine for severe pain that persisted beyond 24 hours. Five children (3 to 12 years) had pain scores ≤2 at 24 hours and were discharged within 4 days of admission. Ten had pain scores >2 at 24 hours following admission and required > 4 days of hospitalization ($p<.005$). These findings suggest that pain is not well-controlled in the majority of patients after initiation of this protocol. Mean pain intensity scores before initiation of the protocol, and at one hour and two hours, although reported to be recorded, were not included in this analysis. Only the means of the first ten pain intensity scores (see Table 1) were compared between younger (3 to 12 years, n=9) and older children (13 to 18 years, n=8), and among children who experienced only extremity pain (n=6), only abdominal, back, and chest pain (n=4), and diffuse pain (n=7). In addition, no other analysis was reported regarding changes in pain intensity over the course of the hospitalization. Changes in pain location surface area, the child's perception of pain relief, or functional status may be additional indicators of the effectiveness of this pain management protocol. However, these outcomes were not measured or observed in this study.

In a non-research based report, another pain management protocol was described (Morrison, 1991). Initial pain management consisted of a bolus of intravenous morphine (0.1 mg/kg/dose, maximum dose 8 mg) every 2 hours "prn" for severe pain (not defined by a measure of pain intensity). If eight or more bolus doses were needed in any 24 hour period, the patient was placed on a continuous infusion with additional boluses via PCA (0.1mg/kg loading dose, 0.05 mg/kg/hr basal rate, 0.03mg/kg/dose PCA dose with a 20 minute lockout, total maximum 0.14 mg/kg/hour).

If the patient remained in pain (pain intensity measure not defined) after 3 to 4 hours, or required 1 or 2 more additional PCA boluses every hour, an additional bolus of 0.05 mg/kg was given, and the continuous infusion rate was increased by 0.02 to 0.04 mg/kg/hour. Ibuprofen (10 mg/kg PO to a maximum dose of 800 mg every 4 hours) could be used with morphine, particularly if musculoskeletal pain was evident. Docusate was also prescribed on admission to prevent opioid-induced constipation. Hydroxyzine or diphenhydramine in standard dosing recommendations was given for itching.

In contrast to the pain management protocol described by Sporrer and colleagues (Sporrer et al., 1994), the dose was not weaned when the patient became comfortable at 24 hours, because the weaning process resulted in a return of pain and increased anxiety. The infusion was maintained for at least 24 to 36 hours or until the return of a normal affect suggested that pain was less and could be managed with oral analgesics. The duration of prior painful events experienced by the patient was used to guide the weaning plan. The infusion could be stopped without weaning if oral

analgesics (acetaminophen with codeine or equivalent) were administered one hour before discontinuing the infusion. The infusion was resumed if moderate to severe pain returned. Oral analgesics were continued every 4 hours for 12 to 24 hours after stopping the infusion, then, "prn". Some patients were discharged at this point, even if they were still in some pain. Full doses of acetaminophen with codeine could be alternated with ibuprofen so that some medication was given every 2 hours. A research study to determine the effectiveness of this pain management protocol was not reported.

In summary, research on pain management in children with sickle cell disease predominantly described safety (in terms of dosage, side effects, or complications), utilization patterns, and efficacy in relationship to pain intensity. The effect of pain management strategies on outcomes other than pain intensity, such as pain location, pain quality, pain relief, and function were not examined. Furthermore, no study was found that utilized a longitudinal design to examine changes in pharmacologic interventions and their relationship with changes in children's self-report of pain relief, pain intensity, pain quality, pain location surface area, and function, as the pain evolved throughout the course of hospitalization. In addition, the effectiveness of pain management protocols that utilized combinations of opioids, nonopiods, and adjuvant analgesics were not examined.

Pain Outcomes

Several outcome measures were used to examine relationships between pharmacologic interventions and patient outcomes. In one study that compared an intermittent versus continous infusion of morphine (Robieux et al., 1992) the

following outcomes were examined: physiological measures (i.e., vital signs, oxygen saturation, pupil diameter, Glasgow Coma Scores (GCS), presence of side effects (i.e., nausea, vomiting, sweating, pruritus), and signs of opioid toxicity (i.e., drowsiness or coma, pinpoint pupils, emesis, sweating or pruritis, decreased respiratory rate <12/min). Two studies used sedation rating scales to determine safety of transdermal fentanyl (Christensen, Wang, Harris, Eades, & Williams, 1996) and to compare the effects of ketorolac versus meperidine (Grisham & Vichinsky, 1996).

In two studies that used PCA (Shapiro & Cohen, 1993) other outcomes were used: ratios of average number of PCA attempts to injections, number of PCA attempts to injections on day of maximum use, amount of drug actually delivered to total dose allowed on day of maximum use (Shapiro & Cohen, 1993), total amount of morphine used during hospitalization, total morphine on hours 1 to 24, total morphine on hours 25 to 48, total days on PCA, length of hospital stay, and costs (Trentadue et al., 1998). Table 2 provides a summary of findings from these studies.

In one retrospective study that examined efficacy and safety of epidural fentanyl for management of severe pain unresponsive to a standard regimen (Yaster, Tobin, Billett, Casella, & Dover, 1994), the amount of opioid used, mean duration of opioid use, and presence of complications such as those related to: catheter placement (i.e., inadvertent dural puncture, catheter migration, local and systemic infection, inability to place catheter correctly in the epidural space); clinical status (acute chest, infections); and anesthesia (seizures, cardiovascular collapse, respiratory depression, tachyphylaxis, elevated lidocaine plasma levels) were examined (Yaster et al., 1994). In another study that examined the use of adjuvants, the presence of toxic reactions to

steroids such as, headache, psychological disturbances, hypertension, cardiac dysrhythmia, infections complications (Griffin, McIntire, & Buchanan, 1994) were used as outcome measures. No studies were found that examined change in child's perceptions of pain relief and functional status (i.e., sleeping, eating, activity level) as outcome measures of pharmacologic interventions or as outcome measures related to the pain experience of children who are hospitalized for a vaso-occlusive episode.

Functional Status

Shapiro and colleagues (1990) explored functional status (sleeping and activity) in children (6 to 16 years, n=15) who were followed for four months prior to a study examining the efficacy of self-hypnosis versus education in modifying the experience and effect of vaso-occlusive pain on activities of daily living (Dinges et al., 1997). Quantity (length) and quality (good versus bad) of sleep on nights prior to and following vaso-occlusive pain days, relative to nights following pain free days were evaluated. Both the quantity and quality of sleep was more likely to be disturbed on nights before (36%) and after (42%) vaso-occlusive pain days relative to pain free days. Activity was evaluated in terms of school attendance and time spent outdoors. Patients did not attend school on 48% of days (n=1144 diary days) they experienced vaso-occlusive pain and did not go outside on 42% of the days they experienced vaso-occlusive pain (Shapiro et al., 1990).

In another report (Shapiro et al., 1995), when children (8 to 17 years, n=18) were enrolled in a study of the natural history of sickle cell-related pain, and of the efficacy of self-hypnosis as an intervention, sleep and activity in relation to school attendance were evaluated. Patients reported poor sleep on an average of 43% of

days with pain, compared to only 3% of days without pain ($z=3.57$, $p<.001$). Sleep duration was significantly less on nights when pain occurred relative to nights without pain ($z=3.62$, $p<.001$). Patients missed school on 41% of the days when they reported pain, compared to an average of 9% on days without pain ($z=-3.29$; $p<.001$).

Gil and colleagues (1991) asked parents of children (7 to 17 years, n=72) to estimate the percentage of time during painful episodes their children reduced involvement in household, school, and social activities by marking three 100-millimeter lines from 0% (do not cut back at all) to 100% (cut back completely). Parents reported frequent painful episodes (mean 5.92, SD=8.55 episodes) in the previous 9 months that resulted in reductions in household activity (71.56%, SD=35.86), school activity (53.40%, SD=36.76), and social activity (59.22%, SD=39.54) and required regular contact with health care services.

In a follow-up study (Gil et al., 1993), parents were asked to estimate "uptime" (the number of hours their children (7 to 18 years, n=70) spent-up (such as standing, walking, and sitting) versus "downtime" (the number of hours their children spent down, such as reclining) on a day during painful episodes. Parents were also asked to estimate the percentage of time per day during painful episodes that their children reduced involvement in school, household, and social activities by marking three 100 millimeter lines from 0% (do not cut back at all) to 100% (cut back completely). Only the results of the regressional analysis related to coping strategies were presented. Baseline coping strategy factors accounted for signficant proportions of the variance (up to 15%) in subsequent school, household, and social activity reductions. Children who scored high on coping attempts had less activity reduction

during painful episodes and had greater amounts of uptime. Actual percentages of "uptime" and "downtime" were not reported.

Walco and Dampier (1990) asked parents of children (age 5.4 to 15.9 years, n=18) during a regularly scheduled appointment in the sickle cell clinic to rate the child's activities on a 5-point scale (never, rarely, sometimes, often, always) in terms of how they perceived them to be influenced by pain. Parents rated pain as interfering with sleeping (29% sometimes, 29% often, 20% always), favorite activities (40% sometimes, 14% often, 26% always), school attendance (23% sometimes, 14% often, 37% always), sports (34% sometimes, 20% often, 29% always), and appetite (29% sometimes, 17% often, 26% always). There were no other studies that reported changes in appetite or eating during painful episodes.

In summary research related to the pain experience, pain management, and pain outcomes of children with sickle cell disease who are hospitalized for vaso-occlusive pain is very limited. No study was found that described changes in three pain characteristics (i.e., intensity, location, quality), pharmacologic pain management strategies, children's perception of pain relief, and functional status (i.e., sleeping, eating, activity level) during the progression of the painful episode. In addition, no research was found that described changes in physical signs and symptoms and changes in complete blood counts that are associated with clinical manifestations of pain in children with sickle cell disease.

CHAPTER 3

METHODOLOGY

Research Design

A descriptive longitudinal design was used to: describe changes in three pain characteristics (i.e., intensity, location, quality), functional status (i.e. sleeping, eating, activity level), presence or absence of selected signs and symptoms associated with vaso-occlusion, changes in CBC values (i.e., hemoglobin, hematocrit, white blood cell count, platelet count, reticulocyte count), pharmacologic interventions, and children's self-reports of pain relief from pharmacologic interventions during hospitalization. Data collection occurred once every evening, from day one of hospitalization until day of discharge. This study was approved by the Committee on Human Research (CHR) at the University of California San Francisco (H7025-17123-01) and by the Medical Research Committee and Institutional Review Board at Children's Hospital Oakland (see Appendix F for letters of approval).

Research Setting

This study was conducted in a large nonprofit children's medical center serving 56 counties in northern California. This medical center has 205 total licensed hospital beds (70 critical care licensed beds —23 pediatric intensive care and 47 intensive care nursery), serving more than 1700 patients per year with an average daily census of 151 patients. Currently, the Sickle Cell Center follows about 500 children with sickle cell disease. Based on the 1998 Sickle Cell Center grant report, there were 1539 clinic visits, 557 emergency department (ED) visits, and 491 hospitalizations, with 188 inpatient visits for vaso-occlusive episodes (VOE),

representing 88 patients with sickle cell disease. The number of children between the ages of 5 to 19 years was not reported. Based on the 1998 grant report, the mean length of hospital stay for a VOE was 5.52 days (SD=4.45, range 0 to 28 days). Data collection occurred in the 26-bed hematology/oncology unit.

Sample

Study participants were children with sickle cell disease, 5 to 19 years of age who were experiencing pain. Children were selected based on the following criteria: 1) admission to the acute care unit for a vaso-occlusive painful episode within the previous 24 hours; 2) English-speaking; parental consent for the child to participate in the study; 3) child assent to participate in the study; and 4) no prior history of neurological impairments (i.e., visual or hearing deficits, motor function deficit, and developmental delay), or had previously enrolled in this study three times.

Children, 5 to 19 years, with sickle cell disease were excluded if: 1) they were not having pain at time of recruitment; 2) pain was not due to vaso-occlusive episode; 3) they were non-English-speaking; 4) parents refused to participate; 5) child refused to participate; 6) they had prior history of neurological impairments (i.e., visual or hearing deficits, motor function deficit, and developmental delay), or 7) had previously enrolled in this study three times.

Sample size calculations were based on a test to detect a significant slope in values during the progression of the painful episode. It was expected that a small change in values (as indicated by a slope d=.30) would be detected. An alpha of 0.05 level test with power of 0.80, and a conservative value of rho=0.0 as the measure of likeness of repeated pair measurements within the same child and preliminary data

from Conner-Warren (1996) (σ^2=1.3) were used in the power calculations. Power calculations in Diggle, Liang and Zeger (1990) showed that a sample of approximately 30 patient admissions observed for an average of 5.5 days would have sufficient power to detect a small change in variables over time.

Variables and Instruments

Demographics and Medical Information & Child/Parent Interview Form

The demographics and medical information form (Appendix G) is a four-page fill in the blank data collection tool for obtaining the following information: child's weight in kilograms, date of birth, hemoglobin phenotype (SS, SC, Sβ, etc), gender, date and reason for hospitalization (e.g., fever, pneumonia, pain, acute chest syndrome, splenic sequestration, infection), and date since last seen in ED, Clinic, Day Hospital, and/or Acute Care Unit. In addition, information related to previous hospitalizations and complications (stroke, splenic sequestration, acute chest syndrome, rib infarcts, avascular necrosis, leg ulcers, infections, pneumonia, duodenal ulcers, pancreatitis, cholecystitis, psychotic disorders, and any other illnesses and conditions) in the past 12 months; number of times and reasons for clinic visits in the past 12 months; the number of times and reasons for ED visits in the past 12 months; and the number of times and reasons for hospitalizations in the past 12 months were recorded.

Information related to multidisciplinary interventions (e.g., Physical Therapist, Psychologist, Child Life Volunteer, Play Therapist, Social Worker, Home/Hospital Teacher) if the child was meeting with different professionals on a regular basis during the hospitalization, and history of disease related interventions

(e.g., chronic packed red blood cell transfusion therapy, exchange transfusion, hydroxyurea, desferal, bone marrow transplant) were also collected on this form.

Finally, information from the accompanying parent or guardian about when the painful episode began; any signs and symptoms noted before the child complained of pain; when the pain actually started; a rating of pain intensity using the Oucher Pain Scale of the child's pain when it started; whether pain started gradually, intermittently, or suddenly; once pain started whether it was constant or off and on; a rating of pain intensity using the Oucher Pain Scale of child's pain at time of admission; the name, amount, and frequency of pain medications given prior to admission; and the date and time when the first call was made to the clinic, physician, or nurse were also noted.

Validity and Reliability: Content validity of the instrument was determined by review of a panel of expert clinicians and researchers.

Method of Administration: The researcher completed the Demographics and Medical Information Sheet and the Child/Parent Interview Form within the 24 hours of the child's admission to the hematology/oncology unit.

Oucher Pain Scale: Measure of Pain Intensity

The Oucher Pain Scale consists of a poster showing six photographs on the right side and a 0 to 100 scale marked off in tens on the left side. The photographs show the face of an African-American child with the pictures arranged in increasing levels of discomfort. It has been used by children 3 to 12 years of age (Beyer, 1986; Beyer, 1988; Beyer, 1990; Beyer, 1992; Beyer, 1998). Children used the Oucher Pain Scale by selecting a photograph or number that most closely represented the level of

pain intensity they were experiencing. Children who were able to count to 100 by ones or tens and who understood, for example, that 71 is greater than 43, also used the numeric scale (Beyer, 1986; Beyer, 1988; Beyer, 1990; Beyer, 1992; Beyer, 1998).

Validity and Reliability: Construct validity of the African-American and Hispanic versions of the Oucher Scale was examined in 104 children (52 African-American, 52 Hispanic, 48 girls, 56 boys, ages three to twelve years) (Beyer, 1998). Children were randomly assigned, before or after surgery, to data collection with two pain instruments, the Oucher scale and the Analogue Chromatic Continuous Scale (ACCS) (Grossi, 1985; Grossi, 1983), and a fear measure, Child Medical Fear Scale (CMFS) (Broome, 1987; Broome, 1988).

Strong positive correlations were found between the scores on the Oucher Pain Scale and the ACCS, ranging from .89 to .97 (p=.001). There were no differences in pain scores for older subjects using the numeric scales (t (43.35) = 1.35, p=.184) or for younger subjects using the photographic scales of the Oucher Pain Scale according to their ethnicity (Mann-Whitney U=285.8, z=-1.06, p=.291). The Cronbach alpha for the CMFS scale was .79, demonstrating adequate internal consistency reliability. Correlations were low and nonsignificant, ranging between .21 and .33 (p>.05), between the Oucher Pain Scale and the CMFS, in three of the four groups of children. In the Hispanic numeric group, there was a moderately strong relationship between the Oucher and the CMFS, r=.513 (p=.007). There was a significantly moderate correlation between the CMFS and the ACCS (r=.434, p, .027; (Beyer, 1998).

Method of Administration: The researcher asked the child to rate the amount of pain felt now, as well as the worst pain, and the least pain felt during the day and night, using the Oucher Pain Scale. This assessment was done once every evening, from the day of admission until the day the child was discharged home. Responses were recorded on the Data Collection Tool (Appendix H). If the child was 8 years of age or older, was able to count to 100, and was able to distinguish that the number 70 is larger than the number 30, both the photographic and numeric rating scales of the Oucher Pain Scale were used. For the child younger than 8 years of age, only the photographic scale was used. The explanation follows:

> *"This is my poster called OUCHER. It helps children to tell me about their hurt. This child (pointing to the bottom picture) has no hurt, no hurt at all. Here there is a child with just a little bit of hurt (pointing to the second picture). Here is a little more hurt (pointing to the third picture). This one shows even more hurt (pointing to the fourth picture). This one shows a lot of hurt (pointing to the fifth picture) and this one up here shows the biggest hurt you could ever have (pointing to the sixth picture)".*
>
> **Pain now:** *"Point to the picture that shows how much hurt you are having right now".*
>
> **Worst Pain:** *Was there ever a time during the night or day when you had more hurt than what you feel right now?*
>
> If the response was yes: *"Point to the picture that shows how much was the biggest hurt you had at that time?"*

Least Pain: *"Was there ever a time during the night or day when you did not have any hurt or had very small hurt than what you feel right now?"*

If the response was yes: *"Point to the picture that shows how much was the smallest amount of hurt you had?"*

With the older child, the numeric scale was also used and explained as follows:

"0 means no hurt. If your hurt is somewhere in here (pointing to the lower third of the scale between 0-29), it means you have little hurt; if your hurt is somewhere in here (pointing to the upper third of the scale between 70-99), it means you have big hurt. If you point to 100, it means you have the biggest or worst hurt you could ever have".

Pain Now: *"Point to the number (or tell me which number) that is like the hurt you are having right now".*

Worst Pain: *"Was there ever a time during the night or day when you had more pain than what you are having right now"*

If the response was yes: *"Point to the number that is like the worst hurt you had?*

Least Pain: *"Was there ever a time during the night or day when you did not have any pain or less pain than what you are having right now?*

If the response was yes: *Point to the number that is like the smallest hurt you had?*

Adolescent Pediatric Pain Tool (APPT)

The Adolescent Pediatric Pain Tool (APPT) is a one-page, two sided instrument with a front and back body outline on one side (Savedra, 1989; Savedra, 1993; VanCleve, 1993). On the other side is a 100mm word-graphic-rating scale (Tesler, 1991) and a pain descriptor list (Wilkie, 1990). See Appendix B for the instrument, the template, and instructions from the authors.

Validity and Reliability of the Body Outline Diagram of the APPT: Measure of Pain Location. The validity and reliability of the body outline was explored in hospitalized children 4 to 17 years of age (Savedra, 1989; VanCleve, 1993). The body outline used was redrawn from the body outline format of the McGill Pain Questionnaire (Melzack, 1975) to represent an older child's or young adolescent's body. Hair was not included and facial features were drawn to avoid representation of a particular gender or ethnic background. The left and right sides of the body outline are indicated on the front and back views to assist the children when using the figure.

A sample of children with various medical and surgical conditions experiencing pain (n=175; 8 to 17 years, 84F/87 M (Savedra, 1989); and (n=46, 4 to 7 years, 14 M/22F, (VanCleve, 1993) were asked to mark the location of his/her current pain on the body outline provided. Three coders counted the number of sites on each body outline, judged the left/right and front/back reversals, and judged the number of sites corroborated by the clinical evidence. They also judged the agreement or nonagreement between the child's markings and the investigators' markings of the child's pointing for the number and the location of the marks and the surface area

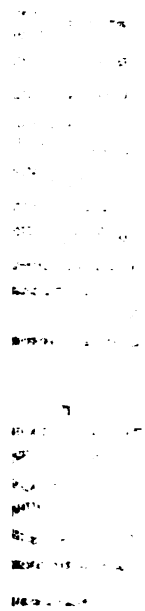
covered (Savedra, 1989). Cohen's Kappa coefficients were calculated to examine the concordance of the three coders' judgments for each possible pair of coders: 1) .71, .55, .58 for the site number agreement; 2) .35, .30, .34 for the location of marks; and 3) .45, .36, .47 for the surface area covered. Alternate forms reliability of the body outline was assessed by the degree of agreement between the child's markings and the child's pointing to pain location as recorded on the second body outline (Savedra, 1989).

Method of Administration: The researcher asked the child to complete the Body Outline Diagram to indicate where they hurt. This procedure was done once every evening, from the day of admission until the day the child was discharged to home. Responses were recorded on the Data Collection Tool (Appendix H). The explanation follows:

> *"When you had the most hurt today, color in the areas on the Body Outline Diagram to show where it was hurting. Make the marks as big or small as the place where the hurt was".*

Reliability and Validity of the Word Graphic Rating Scale of the APPT. On the other side of the Body Outline Diagram is a 100 mm word-graphic rating scale and a pain descriptor list. The three components of the APPT are scored separately. The word-graphic rating scale is the component of the APPT that measures pain intensity and is scored using a preprinted micrometer to measure the number of millimeters from the left side of the scale to the point marked by the child. The numeric value measures the amount of pain the child is experiencing.

Tesler and colleagues (1991) designed a series of studies to select and test the word-graphic rating component of the APPT scale. Five scales (a word graphic rating scale, a visual analogue scale, a graded-graphic rating scale, a magnitude estimation scale or numeric rating scale, and a color scale) were evaluated in four separate phases to determine their validity, reliability, ease of use, preference, and the lack of age, gender, and ethnic biases. The developmental appropriateness and the validity of the five scales were determined by having 958 non-hospitalized children assess the intensity of standardized painful stimuli in an analogue situation. Standardized stimuli were five drawings of a cartoon figure of a child 1) falling off a bicycle, 2) being hit on the head with a baseball, 3) getting an injection, 4) cutting a finger, and 5) misspelling a word in a classroom. The standardized painful stimuli were used because it is difficult to assess validity using clinical pain. Convergent validity of the scales was demonstrated by the moderate to high correlations between each of the five scale ratings for each picture. The average correlation coefficient calculated from Fisher's Z transformations for correlation coefficients, ranged from .66 to .80, $p < .001$.



Construct validity of the word-graphic rating scale (Tesler, 1991) was examined using a repeated measures design with 55 children, ages 8 to 14 years of age, with black, hispanic, and white ethnic backgrounds, and who had neurological, thoracic, orthopedic, urologic, and abdominal surgical procedures. An assumption was made that pain intensity would decrease with postoperative recovery. Data were collected in the morning and in the afternoon starting on postoperative Day 1 for a maximum of 5 days. The mean pain intensity scores on the word graphic rating scale

were highest on the morning of the first postoperative day (67.8) and decreased gradually over the 5 days (20.8 on the fifth morning day). It was concluded that the findings supported the construct validity of the word-graphic rating scale and demonstrated its sensitivity to changes in postoperative pain intensity over time.

Convergent validity and test-reset reliability of the word-graphic rating scale were supported by 35 hospitalized children and adolescents, who reported their current pain intensity, using two copies of the word graphic rating and one copy each of the other four scales mentioned previously (Tesler, 1991). Pearson Product Moment correlations among pairs of scores from the five scales ranged from .68 to .97 (M=.84) and thus supporting convergent validity. Test-retest reliability was supported; the correlation between the two word-graphic rating scales was .91.

Reliability and Validity of the Word Descriptor List of the APPT: Measure of Pain Quality. The word descriptor list of the APPT contains 56 words identified by children as words they knew and would use to describe pain. The 56 words are organized and categorized into thirteen groups that described similar qualities of pain, which included sensory, affective, evaluative, and miscellaneous words.

Tesler and colleagues (1988; 1989) compiled a list of 129 words that children used to describe pain in previous studies (Savedra, 1982; Savedra, 1988; Tesler, 1983). They presented them to 958 students (grades 3 to 12, ages 8 to 17 years, 53% F/47% M) and asked them to sort the words into three categories: words they knew and used to describe pain; words they did not know; and words they knew but did not use to describe pain. They also asked them to assign an intensity value to the words

they used to describe pain, by sorting them into categories denoting small, medium, large, and worst pain. Sixty-seven words (39 sensory, 13 affective, 9 evaluative, and 7 miscellaneous) were selected by 50% or more of the children as words they used to describe pain ([Tesler, 1988; Tesler, 1989, 1989). There were no significant differences in word selection between children previously hospitalized and those with no previous hospitalization (Tesler, 1988; Tesler, 1989).

Using the McGill Pain Questionnaire (Melzack, 1975) as a model, the words were organized theoretically by five clinical nurse specialists. They independently categorized the words into thirteen groups that described similar qualities of pain, which included sensory, affective, evaluative, and miscellaneous words (Wilkie, 1990). Construct validity of the organized word groups (sensory, affective, evaluative, miscellaneous) was examined using exploratory factor analyses to test the unidimensionality of the words and the word groups. The individual words did not represent a single dimension. Four factors in the word groups were extracted with eigenvalues greater than 1 that accounted for 57% of the variance in word selection. A confirmatory factor analysis using LISREL suggested three factors, with factor loadings, ranging from .49 to .59 for the sensory groups, .59 to .85 for the affective groups, and .71 for the evaluative group (Wilkie, 1990).

Method of Administration. The researcher asked the child to complete the Body Outline Diagram to indicate where they hurt. This procedure was done once every evening, from the day of admission until the day the child was discharged home. If the child was able to read, the child was asked to:

"Circle as many words as you want to tell about your hurt when you were having the most hurt you felt today".

If the child was unable to read or did not want to read, the researcher read the words to the child, one group at a time (Appendix B).

Numeric Rating Scale: Measures of Amount of Sleeping, Eating, Activity Level, and Pain Relief

Seven numeric rating scales (Appendix C) were developed to quantify the child's perceptions of amount of sleeping, eating, activity, and amount of relief from pharmacologic interventions during the day and night.

Reliability & Validity: Content validity of the scales was determined by a panel of expert clinicians and researchers.

Method of Administration: The researcher asked the child to rate the amount of sleeping, eating, activity, and amount of relief during the day and night using the 0 to 10 numeric rating scales pictured below. This procedure was done once every evening, from the day of admission until the day the child was discharged home.

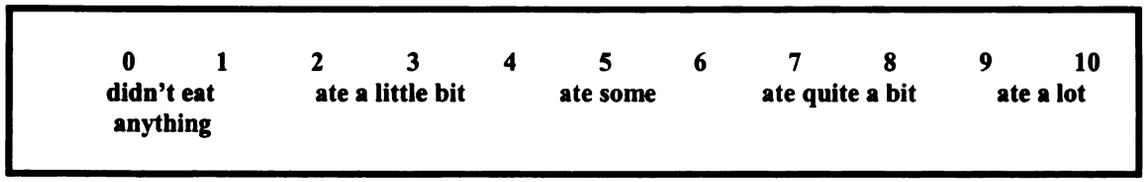
Sleeping – How much sleep did you have last night?

0	1	2	3	4	5	6	7	8	9	10
did not sleep at all		slept a little		slept some			slept quite a bit		slept a lot	

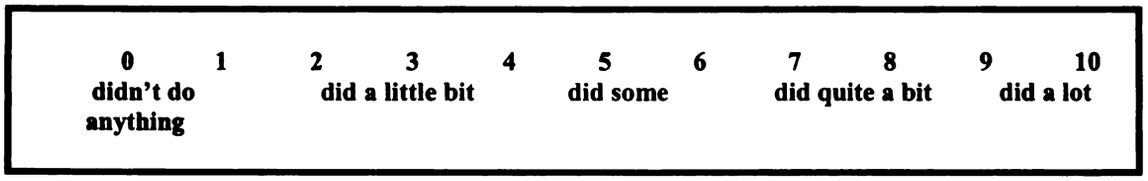
Sleeping – How much sleep did you have during the day?

0	1	2	3	4	5	6	7	8	9	10
did not sleep at all		slept a little		slept some			slept quite a bit		slept a lot	

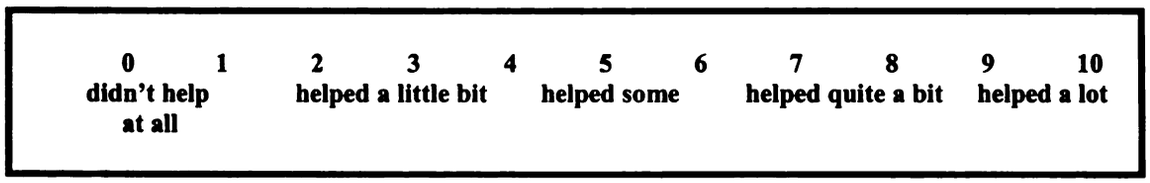
Eating – How much did you eat today?



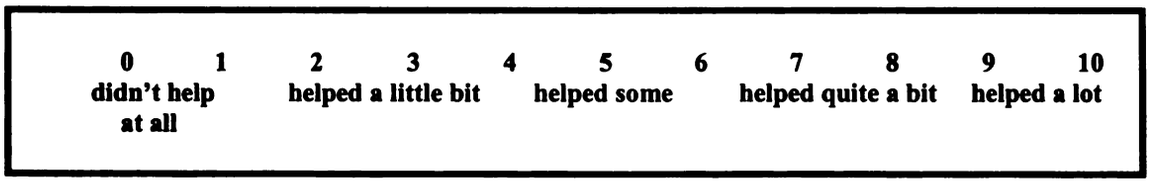
Activity - How much did you do today?



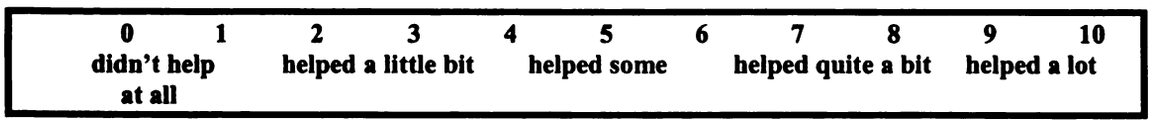
Pain relief during the night – How well did the medicines help you with your hurt during the night?



Pain relief during the day – How well did the medicines help you with your hurt during the day?



Pain relief now – How well are the medicines helping you with your hurt right now?



Signs & Symptoms Checklist – Measure of Physical Signs & Symptoms of Vaso-Occlusion

The signs and symptoms checklist is a list of 25 signs and symptoms that may be associated with a painful vaso-occlusive episode.

Reliability & Validity: Content validity of the checklist was determined by a panel of expert clinicians and researchers.

Method of Administration: The researcher circled from the list (Appendix D) the signs and symptoms that were observed or documented in the nursing flowsheets during each 24 hour period. This procedure was done once every evening, from the day of admission until the day the child was discharged to home.

Circle those that were observed in the last 24 hours:

General

Fever dizzy weak pallor tired yellowing of the eyes
Other _____

Respiratory
change in the way child breathes difficulty with breathing coughing
change in RR change in O2 sats other _____

Musculoskeletal:
swelling of hands/feet joint tenderness joint stiffness
other _____

Gastrointestinal:
Vomiting little or no appetite diarrhea stomach getting bigger
Other _____

Skin:
change in color rashes itching ulcers
Other _____

Total Number of Signs & Symptoms observed _____

Complete Blood Count: Measure of Physiological Markers of the Painful Episode

A complete blood count (CBC) is an enumeration of the cellular elements of the blood and evaluation of red blood indices. The researcher obtained results from the Hospital Information System and recorded the appropriate values on the Data Collection Tool (Appendix H).

WBC	
RBC	
Hgb	
Hct	
RDW	
Plts	
Retics	

This procedure was done once every evening, from the day of admission until the day the child was discharged home.

Medication Quantification Scale (MQS): Measure of Analgesic Use

The Medication Quantification Scale Worksheet (Appendix E) contains spaces to record pharmacologic strategies used for pain management. Space was provided for recording the prescribed amount, frequency, and route/mode of medication administration, and the total dose of each medication administered in 24 hours. Spaces were also provided for calculating the Medication Quantification Scale (MQS) score. The MQS is a method for quantifying medications based on weights assigned by medication class and dosage level (Steedman, 1992). Scores for each medication were summed to provide a quantitative index of total medication usage.

For each pain-related medication, a detriment weight was assigned, based on the potential for producing adverse effects and a dosage level was assigned

(1=subtherapeutic, 2=low therapeutic, 3=high therapeutic, 4=supratherapeutic) based on the recommended daily dosage. All opioids were converted to intravenous morphine equivalents. See appendix E for the list of medications, dose recommendations, and opioid conversion equivalents that were used in the study (Benjamin, 1999; Taketomo, 2001).

Reliability and Validity: Four studies in patients with chronic pain were conducted to determine the reliability and validity of the MQS. Two clinicians who were taught the scoring method and the use of reference tables calculated the total MQS scores for chronic pain patients (n=30) (Steedman, 1992). Interrater reliability was ρ=.985, $p<0.0001$.

MQS scores for 88 patients were also correlated with the clinical judgement of 12 health professionals of the appropriateness of the patients' actual medication profiles (mean $\rho = 0.755$, $p<.0001$). The twelve health care professionals (4 physicians, 4 psychologists, and 4 pharmacists from six academic departments of two institutions (a medical university tertiary care hospital, and a large, private, nonprofit hospital) rated the 8 medication classes using a Likert scale (from 0=no detrimental potential to 6=severe detrimental potential). There was good agreement among evaluators, with the greatest agreement being on the use of strong opioids, and the least agreement being on the use of antidepressants and NSAIDs. And finally, MQS scores for 60 chronic pain patients (30 treated in a chronic pain rehabiliation program and 30 not treated) were obtained at two time points, 12 months apart. MQS scores for the treated group decreased significantly from evaluation to follow-up ($p<0.0001$). MQS scores for the untreated group showed no significant change ($p>0.57$).

Content validity of the modified Medication Quantification Scale was determined by a panel of expert clinicians and researchers.

Method of Administration: Once a day, the researcher reviewed the nursing and PCA flowsheets to determine the dosage, routes, and the number of times the pain medications were administered in the previous 24 hours. These were recorded on the MQS worksheet and an MQS Score was calculated once each day.

Calculation of MQS Scores. Each pain medication for a given patient was given a score based on both the daily dosage and pharmacologic classification of that medication. Scores were summed to yield a total MQS score for that patient. There are 8 classes of medications frequently prescribed for pain and a detriment weight is assigned (Steedman, 1992), based on potential detrimental effects with long-term use (from 1=low potential for adverse effects to 6=high potential for undesirable effects):

Medication Class	Detriment Weight
Acetaminophen/aspirins	1
NSAIDS	2
Antidepressants	2
Skeletal muscle relaxants	3
Benzodiazepines/antianxiolytics	4
Weak Narcotic Analgesics	4
Barbiturates/sedatives	5
Strong Narcotic Analgesics	6

A dosage level is assigned based on recommended daily dosage (Benjamin, 1999; Taketomo, 2001):

Administered Amount	Dosage Level
Subtherapeutic dose (less than recommended dose)	1
Low therapeutic dose (lower half of daily dosage range)	2
High therapeutic dose (upper half of daily dosage range)	3
Supratherapeutic dose (greater than recommended)	4

Opioids were converted to IV morphine equivalents. See appendix E for the list of medications that were received by patients in the study that were used for determination of dosage level and for conversion of opioids to IV morphine equivalents (Benjamin, 1999; Taketomo, 2001). The detriment weight was multiplied by the dosage level to yield an MQS score for each medications and then summed to obtain the total MQS score for each patient once a day.

Procedure

Recruitment and Consent

A consecutive sample was obtained from the hematology/oncology unit at Children's Hospital Oakland. Every evening, starting at 5:00 pm, the researcher generated a list of all children, 5 to 19 years, with sickle cell disease, who met the eligibility criteria and were admitted for a painful episode within the previous 24 hours (see Recruitment and Enrollment Log Form, Appendix I).

The researcher approached the child and the parent/caregiver to explain the study and ask if they would be willing to participate in the study. Assent was obtained from the child and consent was obtained (Appendix J) from the parent/primary caregiver. A list of those children and parents who consented to participate were entered on the enrollment log (Appendix I). If the parent/primary caregiver was not available, a phone call was made to the number provided by the child or in the medical records, and the study was explained. Phone consent was obtained and the consent form was signed the next time the parent/primary caregiver visited the child.

Data Collection

At the time of consent, the researcher interviewed the child and/or parent or primary caregiver about the onset of the painful episode. If the parent was not available, the questions were asked over the phone or when the parent/primary caregiver visited the child within the subsequent 24 hours. The researcher asked the following questions (see Appendix G): 1) When did the pain start? 2) Was there any signs or symptoms you noted before the child complained of pain (the Signs &

Symptoms Checklist was used as a guide and the number of days prior to admission when the sign or symptoms was noted)? 3) On the Oucher pain scale (Both Faces and NRS), how would you rate the child's pain when it started? 4) Did it start gradually, intermittently, or suddenly? 5) Once it started, was the pain constant or off and on? 6) How would you rate your child's pain at the time of admission (on the Oucher Pain Scale)? 7) What medications did your child receive before admission? How much and how often did you give it (for each medication given)? 8) How much did the medications help (using the 0 to 10 numeric rating scale)?

0	1	2	3	4	5	6	7	8	9	10
didn't help at all		helped a little bit			helped some		helped quite a bit			helped a lot

9) Is there anything else you want to tell me about the onset of this episode? and 10) How does this episode compare to the other painful episodes your child has had? Responses were recorded on the Child/Parent Interview Form (Appendix G). The researcher also completed the Demographic and Medical Information Form (Appendix G).

At the time of enrollment and once every evening, until the day the child was discharged, the following occurred. The researcher asked the child to:

- rate current pain, worst pain, and least pain using the Oucher Pain Scale (Appendix A);
- mark the areas on the Body Outline Diagram where s/he experienced the worst pain (Appendix B);

- circle or point to the words on the Word Descriptor List of the Adolescent Pediatric Pain Tool (APPT) that described his/her hurt when s/he was having the worst pain (Appendix B). If the child could not read or did not want to read, the researcher read the words, one group at a time, and asked the child if there was any word in the group that described when it was hurting the most;
- rate the amount s/he slept during the night and during the day, the amount s/he ate and the amount of activity s/he engaged in during the day, and the amount of pain relief s/he felt during the day when the medications for pain were given, using a 0 to 10 numeric rating scale for each outcome measure (Appendix C).

The researcher then observed and asked the child, asked the parent/guardian (if present) and/or the nurse, and reviewed the nursing flowsheets for absence or presence of signs and symptoms associated with the painful vaso-occlusive episode, using the checklist as a guide (Appendix D). The researcher also recorded the results of the CBCs, which were drawn once each day, on the corresponding spaces on the Signs and Symptoms Checklist (Appendix D).

Finally, the researcher reviewed the nursing flowsheets for the name, amount, route, and frequency of pain medications administered in the previous 24 hours and recorded them on the Medication Quantification Scale Worksheet (Appendix E). The total MQS score was calculated once each day until the child was discharged.

Data Analysis

All data were entered in Statistical Package for Social Sciences (SPSS version 10.0) and were converted to SAS (Statistical Analysis System version 8.0). Descriptive statitistics were used to describe demographic variables. Longitudinal data analysis using the random effects model (Diggle, 1994; Littell, 1996) was used to estimate regression coefficients (y-intercepts and slopes). Y-intercepts represent the scores on day 1, which is the day of recruitment and enrollment in the study, and which occurred within 24 hours of admission to the hematology/oncology unit. The slopes represent the amount of change, either a decrease (negative slope $\beta < 0$), increase (positive slope $\beta > 0$), or no change (slope $\beta=0$) in scores during the entire hospitalization (from day 1 to day of discharge). A p value $\leq .05$ indicates a slope β that is significantly different from 0 (Null Ho: $\beta \neq 0$) and represents either a significant increase (positive slope) or decrease (negative slope) in values over time. A p value $>.05$ indicates a slope that is not significantly different from 0 (Null Ho: $\beta=0$) and represents no change in scores over time.

Pearson's product-moment correlation coefficients (r) were calculated to describe the relationships between slopes (e.g. slopes of pain intensity and pain location surface area, CBC values, MQS scores, and pain relief scores). The correlation coefficient (r) indicates the strength and direction of the relationship between two variables. Correlation coefficients can range from –1 (one variable tends to increase as the other decreases) to +1 (both variables tend to increase or decrease together). A correlation coefficient value closer to $\pm$ 1 indicates a strong relationship, while values closer to 0 indicate a weak or no relationship between two variables. A p value $\leq .05$

indicates a significant relationship (Null Ho: $r \neq 0$) and a p value > .05 indicates no significant relationship (Null Ho: $r = 0$) between two variables.

Analysis Plan for Specific Aims

Specific Aim 1. To describe changes in three pain characteristics (i.e., intensity, location, quality) during hospitalization.

Pain intensity. Y-intercepts, indicating the current, worst, and least pain intensity on day 1, and slopes, indicating the amount of change in the current, worst, and least pain during hospitalization, were calculated for the pain intensity scores obtained using the Oucher NRS.

Pain Location. The number of body areas marked on the body outline diagram (BOD) of the Adolescent Pediatric Pain Tool (APPT, see Appendix B), was counted each day, using the BOD template that accompanied the APPT instructions (figure 1). There are 43 areas and each area is counted as 1 site. One of the following categories were assigned for each APPT assessment of pain location on day 1: 1 = extremity pain only, 2 = chest, back, abdominal pain only, 3 = head and neck pain only, or 4= diffuse pain. Frequency distributions were used to describe the most frequently marked areas on day 1 and descriptive statistics were used to describe the number of body areas marked on the BOD.

In addition to counting the number of body sites, the surface area of the marked sites on the BOD were also measured each day, using a standard millimeter ruler. The longest width of the marked area was multiplied by the longest height of the marked area to get a total body surface area in square millimeters (mm^2). Y-intercepts, representing the total surface area (in mm^2) of pain location on the BOD

on day 1, and the slopes, representing change in the total surface area of pain location during hospitalization were calculated.

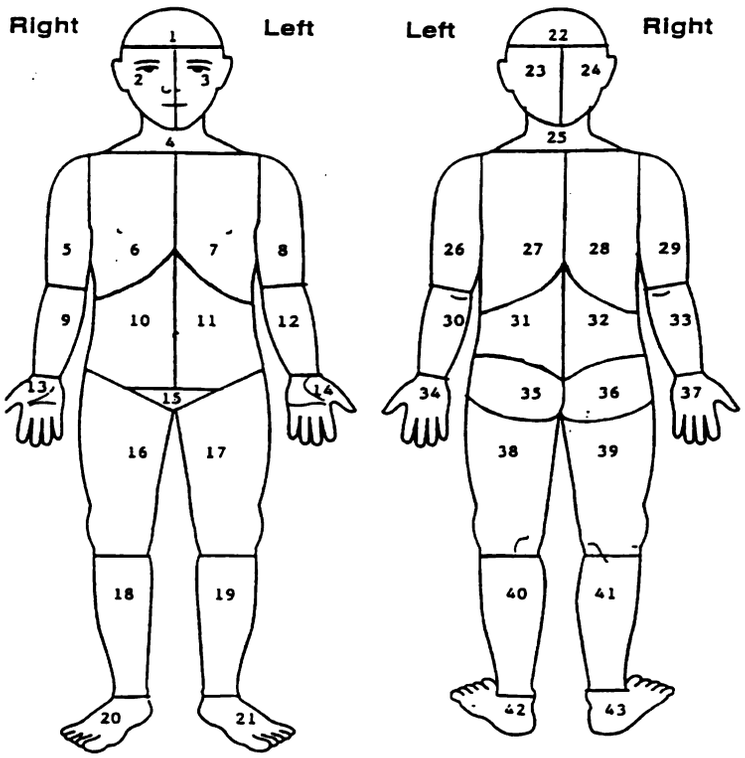


Figure 1: BOD Areas of the APPT

Pain Quality. The total number of words on the word descriptor list of the APPT was counted each day. Scores ranged from 0 to 56. The number of words selected in each of the three categories were also counted each day: evaluative (0-8), sensory (0-37), and affective (0-11), and frequency distributions were calculated (Savedra et al., 1993).

Specific Aim 2. To describe changes in functional status (i.e., sleeping, eating, activity level) during hospitalization.

Y-intercepts, indicating the amount of sleeping at nighttime, sleeping at daytime, eating, and activity level on day 1, and slopes, indicating the amount of change in sleeping, eating, and activity level during hospitalization, were calculated for the sleeping, eating, and activity level scores obtained using the 0 to 10 NRS.

Specific Aim 3. To describe changes in the presence or absence of selected signs and symptoms associated with VOE during hospitalization.

The total number of signs and symptoms were counted each day from a list of 25 signs and symptoms (see Appendix D). Frequency distributions were used to describe the most frequently observed signs and symptoms on day 1. Y-intercepts indicating the number of signs and symptoms on day 1, and slopes indicating changes in the number of signs and symptoms during hospitalization were calculated.

Specific Aim 4. To describe changes in CBC values (i.e., red blood cells, hemoglobin, hematocrit, white blood cell count, platelet count, reticulocyte count) during hospitalization.

Y intercepts indicating the values of red blood cells, hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte counts on day 1, and slopes indicating changes in these values during hospitalization were calculated.

Specific Aim 5: To describe the relationships between changes in pain intensity and changes in pain location surface area during hospitalization.

Pearson product moment correlation (*r*) coefficients were calculated for the slopes of current pain intensity and pain location surface area, and for the slopes of worst pain intensity and pain location surface area.

Specific Aim 6: To describe the relationship between changes in pain intensity and changes in the values of hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte count during hospitalization.

Pearson correlation (*r*) coefficients were calculated for slopes of current pain intensity and hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte count to describe relationships between changes in current pain intensity and each of the CBC values. Pearson correlation (*r*) coefficients were also calculated for slopes of worst pain intensity and each of the CBC values to describe relationships between worst pain intensity and each of the CBC values.

Specific Aim 7. To describe changes in pharmacologic pain management strategies during hospitalization.

Descriptive statistics were used to describe the amount of morphine that was administered at subtherapeutic (less than recommended dose), low therapeutic (lower half of daily dosage range), high therapeutic (upper half of daily dosage range), and supratherapeutic levels (greater than recommended) (Benjamin, 1999; Steedman, 1992; Taketomo, 2001) and to describe the most frequently used co-analgesics on day

1. Y-intercepts indicating the total prescribed MQS score, total administered MQS score, total prescribed morphine dose, total administered morphine dose, and percent administered over prescribed morphine dose, on day 1, and slopes indicating changes in these values during hospitalization were calculated.

Specific Aim 8: To describe the relationship between changes in children's self-reports of pain relief and changes in pharmacologic interventions during hospitalization.

Y-intercepts indicating pain relief at daytime, pain relief at nighttime, pain relief now on day 1, and slopes indicating changes in these values during hospitalization were calculated on scores obtained using the 0 to 10 NRS. To determine relationships between changes in child's self-report of pain relief and changes in pharmacologic interventions during hospitalization, Pearson product moment correlation (r) coefficients were calculated for slopes of:

- pain relief at daytime and total dose of morphine administered
- pain relief at daytime and percent of morphine dose administered versus prescribed
- pain relief at nighttime and total dose of morphine administered
- pain relief at nighttime and percent of the morphine dose administered versus prescribed
- pain relief now and total dose of morphine administered, and
- pain relief now and percent of the morphine dose administered versus prescribed.

Specific Aim 9. To describe the relationship between changes in three pain characteristics (i.e., intensity, location, quality) and pharmacologic interventions during hospitalization.

To describe relationships between changes in pain characteristics and pharmacologic interventions, Pearson product moment correlation (*r*) coefficients were calculated for slopes of:

Pain intensity and Pharmacologic Interventions

- current pain intensity and Total MQS Score administered
- current pain intensity and total morphine dose administered
- current pain intensity and percent of the morphine dose administered
- worst pain intensity and Total MQS Score administered
- worst pain intensity and total morphine dose administered
- worst pain intensity and percent of morphine dose administered versus prescribed

Pain Location and Pharmacologic Interventions

- total number of BOD areas marked and Total MQS Score administered
- total number of BOD areas marked and total dose of morphine administered
- total number of BOD areas marked and percent of total dose of morphine administered versus prescribed
- pain location surface area and Total MQS Score administered

- pain location surface area and total dose of morphine administered
- pain location surface area and percent of total dose of morphine administered versus prescribed

Pain Quality and Pharmacologic Interventions

- total number of word descriptors and Total MQS Score administered
- total number of word descriptors and total dose of morphine administered
- and total number of word descriptors and percent of total dose of morphine administered versus prescribed.

CHAPTER 4

RESULTS

This chapter describes the sample demographics and the pre-hospital experience of children with sickle cell disease who were hospitalized with a vaso-occlusive painful episode in the hematology/oncology unit of a children's hospital medical center during the study period. Changes in three pain characteristics (i.e., intensity, location, quality), functional status (i.e., sleeping, eating, activity level), presence or absence of selected signs and symptoms associated with a vaso-occlusive painful episode, changes in CBC values (i.e., red blood cells (RBC), hemoglobin (Hgb), hematocrit (Hct), white blood cell count (WBC), platelet count, reticulocyte count), pharmacologic interventions, and children's self-reports of pain relief from pharmacologic interventions during hospitalization are described. The results are organized according to the specific aims of the study.

Sample Demographics

Between July 26, 2000 and April 30, 2001, 27 patients with sickle cell disease were admitted to the hematology/oncology unit for painful vaso-occlusive episodes, gave assent, and had parents who gave consent for them to participate in the study. These patients had a total of 40 admissions for painful episodes during this time period. All patients indicated that they were experiencing pain at time of recruitment, which occurred within 24 hours of admission.

The characteristics of the sample are summarized in Table 1. The majority of the patients (59.3%) were male with an average age of 13.6 years. The hemoglobin

phenotype was predominantly HgbSS (77.8%). The onset of pain was on average 4.48days prior to admission and a health care provider was contacted on average about 2.59 days prior to admission. For the majority of the patients the point of first contact was either the Sickle Cell Clinic (48.1%) or the Emergency Department (ED; 48.1%). Patients had a mean of 2.85 ED visits and a mean of 6.27 Sickle Cell Clinic visits in the past twelve months. The mean length of stay during enrollment in the study was 5.85 days (see Table 2). They had a mean of 2.72 hospitalizations during the past twelve months. The majority had a history of acute chest syndrome (66.7%), pneumonia (55.6%), and infections (40.7%), and some (33.3%) were receiving hydroxyurea.

Table 1
Sample Characteristics (N=27)

Age	Mean ± SD	13.56 ± 4.34
	Range	5 to 19 years
Gender		
	Male	16 (59.3%)
	Female	11 (40.7%)
Hemoglobin phenotype		
	SS	21 (77.8%)
	SC	4 (14.8%)
	S beta thal	2 (7.4%)
Number of Days Prior to Admission when Patient First Felt Pain*		
	Mean	4.48 ± 3.58 days
	Range	1 to 14 days
Number of Days Prior to Admission when Health Care Provider was First Contacted*		
	Mean	2.59 ± 2.24 days
	Range	1 to 10 days
Point of First Contact*		
	Sickle Cell Clinic	13 (48.1%)
	Emergency Department	13 (48.1%)
	Day Hospital	1 (3.8%)
Number of ER Visits in the Past 12 Months		
	Mean	2.85 ± 2.41 times
	Range	0 to 10 times
Number of Sickle Cell Clinic Visits in the Past 12 Months		
	Mean	6.27 ± 4.38 times
	Range	0 to 17 times

*Data from first admission

Table 2
History of Hospitalizations, Sickle Cell Related Complications, and Sickle Cell Related Treatments (N=27)

Total Length of Stay During Enrollment in Study

Mean	5.85 ± 2.13 days
Range	3 to 11 days

Number of Hospitalizations in the Past 12 months

Mean	2.72 ± 2.48 times
Range	0 to 10 times

Total Number of Days of Hospitalization in the Past 12 months

Mean	13.71 ± 14.46 days
Range	0 to 59 days

History of Sickle Cell Related Complications

Acute chest syndrome	18 (66.7%)
Pneumonia	15 (55.6%)
Infections	11 (40.7%)
Cholecystitis	7 (25.9%)
Splenic sequestration	5 (18.5%)
Avascular necrosis	3 (11.1%)
Leg ulcers	2 (7.4%)
Rib infarcts	1 (3.7%)
Stroke	2 (7.4%)
Duodenal ulcers	1 (3.7%)
Other illnesses and conditions	10 (39.1%)

History of Sickle Cell Related Treatments

Hydroxyurea	9 (33.3%)
Packed red blood cell transfusions	4 (14.8%)
Exchange transfusions	3 (11.1%)
Desferal	2 (7.4%)
Arginine	2 (7.4%)

Pre-Hospital Experience

The patient or the parent was interviewed within 24 hours of admission to the acute care unit regarding the pain experience and management of pain prior to admission to the hospital. The majority (59.3%) described the onset of pain as sudden and that pain continued to be constant for 70.4% of patients from the time of onset until admission to the hospital. The majority (66.7%) also indicated that the onset of the painful episode was similar to previous episodes. The mean pain intensity rating at onset was 60.37 ± 26.92 on the Oucher Numeric Rating Scale (NRS), with more than a third of the patients (40.8%) rating their pain at ≥ 80 on the NRS.

Signs and symptoms associated with VOE were observed by patients and/or parents on average 4.30 ± 3.64 days (range 0 to 14 days) prior to admission. The mean number of signs and symptoms associated with VOE were 3.93 ± 2.99 (range 1 to12) with 85.2% showing general signs and symptoms such as tiredness, dizziness, weakness, yellowing of the eyes, and paleness. Some (63.0%) had gastrointestinal symptoms (e.g., nausea, vomiting, change in appetite). More than half (51.9%) had respiratory symptoms (e.g., difficulty with breathing, coughing, change in the way child breathes) and about one third (33.3%) had musculoskeletal symptoms (e.g., swelling of hands/feet, tenderness or stiffness in joints). A few (25.0%) had other signs and symptoms such as change in skin color (e.g., darkness around the eyes or feet) and itching.

The most common medications used at home to manage pain prior to hospitalization were acetaminophen with 30 mg codeine (48.1%) and ibuprofen (44.4%). A few had used acetaminophen with hydrocodone (14.8%), ketorolac (14.8%), acetaminophen (14.8%), naproxen (7.4%), or acetaminophen with oxycodone (3.7%).

The mean pain relief score (0=did not help at all to 10= helped a lot) was 2.33 ± 2.77; the majority (44.4%) indicated that they did not experience relief from these medications.

Some patients (37.0%) spent less than 4 hours in the ED, but the majority (63%) spent 5 to 14 hours in the ED prior to admission. The majority (77.7%) received morphine at a mean dose of 4.6 mg ± 1.56 mg (range 2 to 8 mg) in the ED. With a mean weight of 51.4 kg ± 21.08 range (16.8-111.9 kg), most patients received morphine at subtherapeutic (52.4%) or low therapeutic (42.8%) doses, when compared with the recommended dosages based on weight (Benjamin, 1999; Taketomo, 2001). In addition to morphine, some patients also received ketorolac (40.7%) or both ketorolac and diphenhydramine (33.3%) in the ED.

Specific Aim 1. To describe changes in three pain characteristics (i.e., intensity, location, quality) during hospitalization.

Pain Intensity. Figure 1 presents the mean, current, and least pain intensity scores on day 1 (i.e., the day of admission to the hematology/oncology unit and day of enrollment into the study). On day 1, the mean current pain intensity score was 67.17 ± 19.77 (range 24.49 to 100); the mean worst pain intensity score was 84.61 ± 9.90 (range 63.82 to 100) and the mean least pain score was 55.13 ± 21.22 (range 16.24 to 96.42). About 50% of the episodes on day 1 were associated with a current pain intensity score of >70, a worst pain intensity score of > 80, and a least pain intensity score of > 55 (see Figure 1).

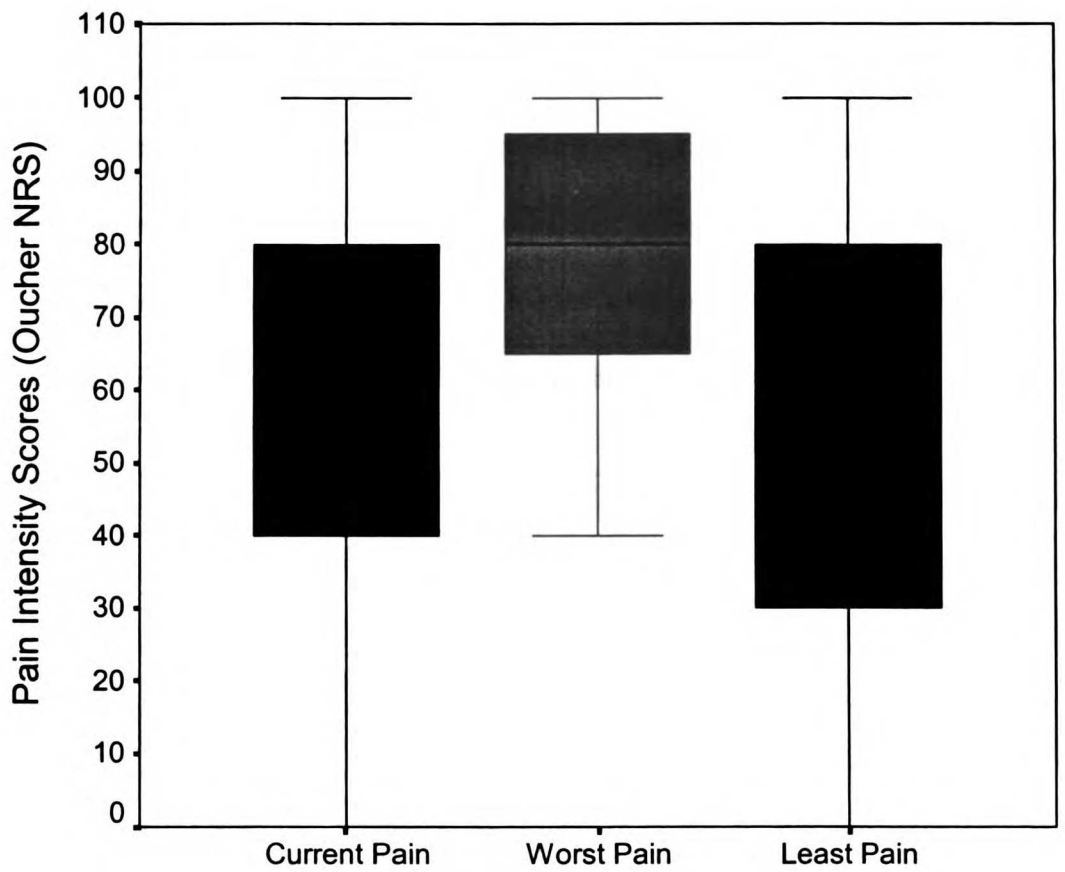


Figure 1. Range of current, worst, and least pain intensity scores on day 1. Shaded area represents 50% of all the pain intensity scores on day 1. Lines outside shaded area represent upper 25% and lower 25% of pain intensity scores on day 1. Line in shaded area represents median pain intensity scores on day 1 (i.e. 50% of all the pain intensity scores are above and below median line).

A significant decrease in current, worst, and least pain intensity scores occurred during hospitalization (see Figure 2). Current pain intensity decreased an average of 5 on the 0 to 100 Oucher NRS (β = -5.26 ± 5.25, p=0.0004) during hospitalization. Worst pain intensity decreased an average of 5 on the 0 to 100 Oucher NRS (β = -5.11 ± 4.76, p=0.0004) during hospitalization and least pain intensity decreased an average of 4 on the 0 to 100 Oucher NRS (β = -3.90 ±, p=0.0009) during hospitalization.

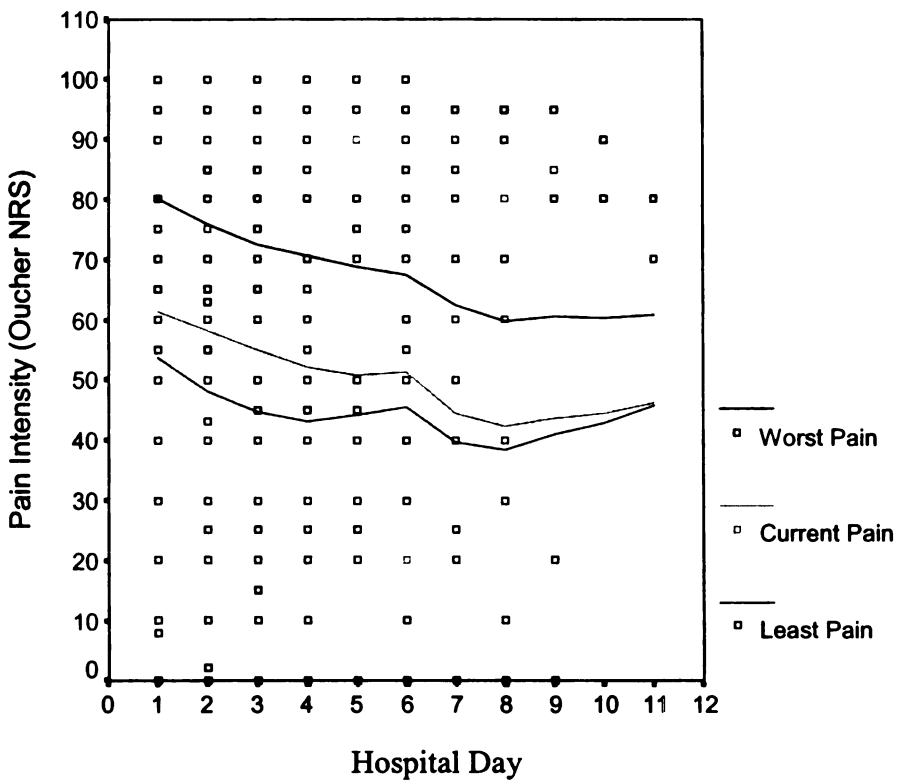
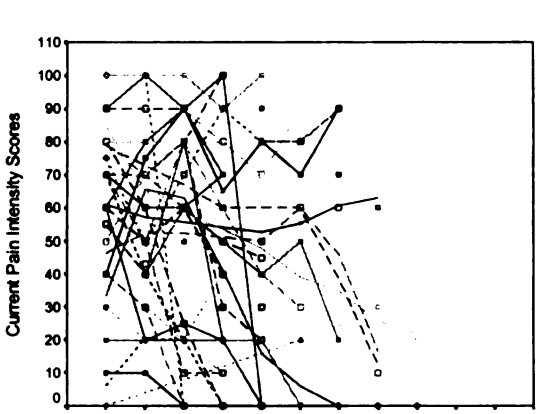
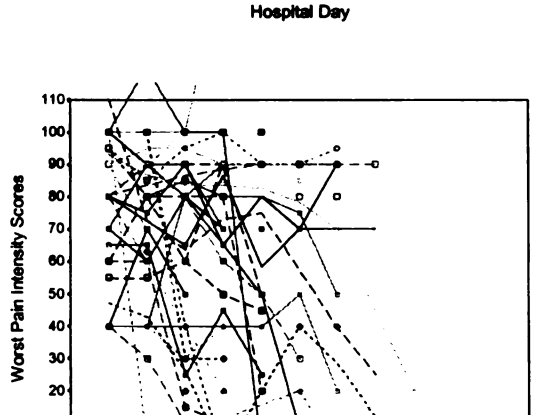


Figure 2. Mean change in current, worst, and least pain intensity scores during hospitalization.

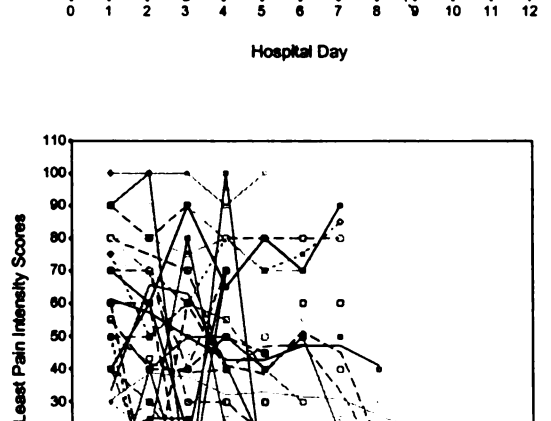
As illustrated in Figure 3, individual changes over time in current, worst, and least pain intensity scores were highly variable.



(a)



(b)



(c)

Figure 3. Individual variations in current (a), worst (b), and least (c) pain intensity scores during hospitalization.

The range in individual variations in change (as represented by slopes) is summarized in Figure 4. Change in current pain intensity showed a range from a maximum decrease of 20 (β = -20.59) to an increase of 3 (β = 3.11) on the 0 to 100 Oucher NRS. Change in worst pain intensity during hospitalization showed a range from a maximum decrease of 15 (β = -14.57) to an increase of 8 (β = 7.99) on the 0 to 100 Oucher NRS. Change in least pain intensity during hospitalization showed a range from a maximum decrease of 12 (β = -11.94) to a small increase of 3 (β = 2.64) on the 0 to 100 Oucher NRS. About 25% of the painful episodes were associated with slopes closer to or greater than 0, suggesting no change or a small increase in current, worst, and least pain intensity scores during hospitalization.

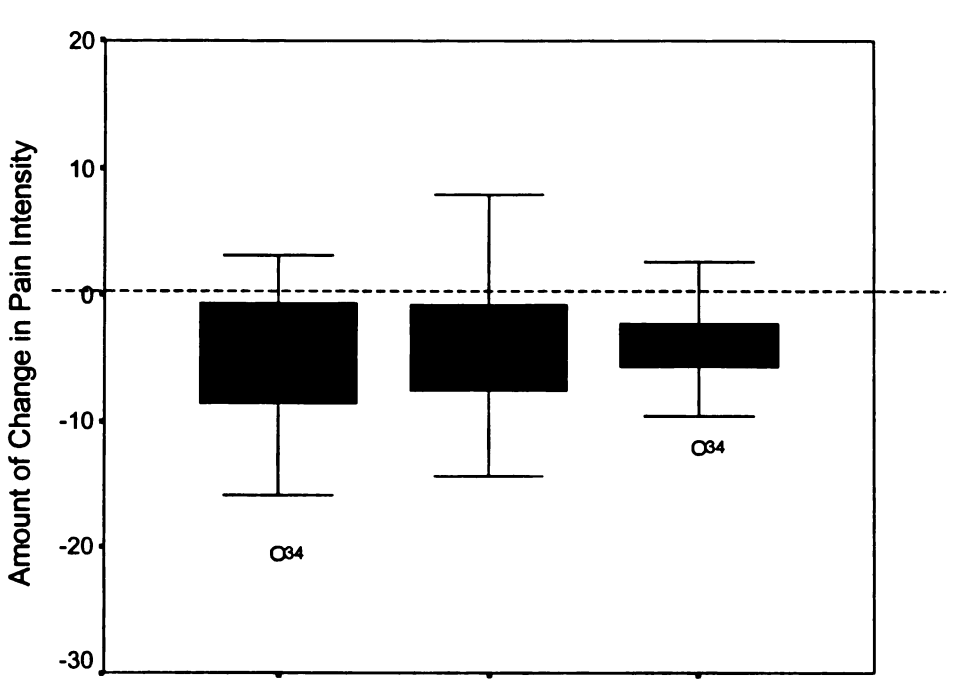


Figure 4. Range of individual variations in changes (β) in current, worst, and least pain intensity scores during hospitalization. Shaded area represents 50% of slopes of pain intensity during hospitalization. Lines outside shaded area represent upper 25% and lower 25% of all slopes. Line in shaded area represents median slope (i.e. 50% of all slopes are above and below median line). Circle with number beyond upper and outer lines represent outliers. β closer to 0 = no change in pain intensity during hospitalization. $\beta < 0$ = decrease in pain intensity during hospitalization. $\beta > 0$ = increase in pain intensity during hospitalization.

Pain Location. The number of body areas marked on the body outline diagram (BOD) of the Adolescent Pediatric Pain Tool (APPT), was counted using the BOD template that accompanied the APPT instructions.

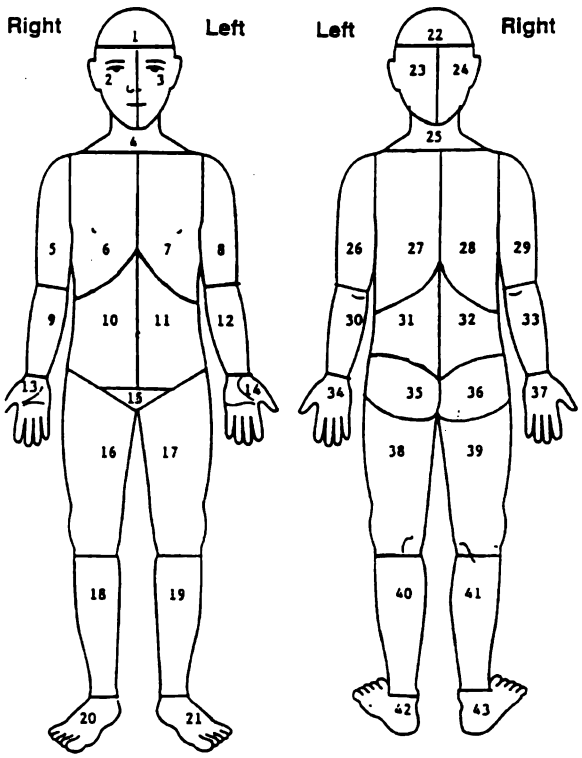


Figure 5. Body areas of the Adolescent Pediatric Pain Tool (Savedra, et al, 1994)

As illustrated in Figure 5, 43 body areas can be marked and each area is counted as 1 site. The APPT was completed each evening. Children were asked to mark where pain was experienced during the day. Each assessment using the BOD was assigned to a category based on the sites that were marked (1 = extremity pain only; 2 = chest, back, abdominal pain only; 3 = head and neck pain only; 4 = diffuse pain, mix of 1, 2, or 3).

The most frequent category marked was category 2 (i.e., the chest, abdomen, and lower back; 55.3%). Approximately 44.7% marked category 3 (i.e., diffuse pain in extremities and chest, abdomen, and lower back) and only 15.4% marked category 1 (i.e., had extremity pain only).

On day 1, the mean number of sites marked on the BOD was 8.0 ± .26 sites (range 7.26 to 8.63 sites). The number of sites decreased slightly on each day of hospitalization (β = -0.41, p=0.005; range β= .22 to β = –1.15).

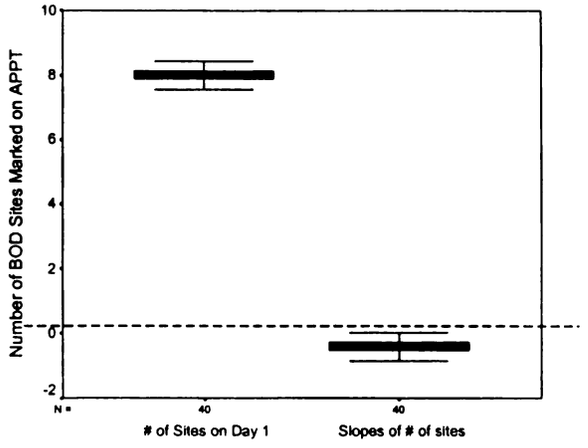


Figure 6. Number of BOD sites marked on the APPT and change in number of BOD sites during hospitalization. Shaded area represents 50% of scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median scores (i.e. 50% of scores are above and below median line). β closer to 0 = no change in total number of BOD sites during hospitalization. $\beta < 0$ = decrease in total number of BOD sites during hospitalization. $\beta > 0$ = increase in total number of BOD sites during hospitalization.

In addition to counting the number of body sites, the surface area of each of the sites was measured using a standard millimeter ruler. The longest width of a marked area was multiplied by the longest height of a marked area to calculate a total body surface area in square millimeters (mm^2). A summary of the total surface area marked on the

BOD for day 1 and the changes in the total surface area (as represented by slopes) that occurred during hospitalization are presented in Figure 7. On day 1, the mean total body surface area marked on the BOD was 1447.28 $mm^2 \pm$ 1337.52 mm^2 (range 207.14 to 6478.62 mm^2). A mean decrease of 59.87 $mm^2 \pm$ 44.98 ($p=.02$; range $\beta = 44.14$ to $\beta = -175.94$) per day was observed during the course of hospitalization.

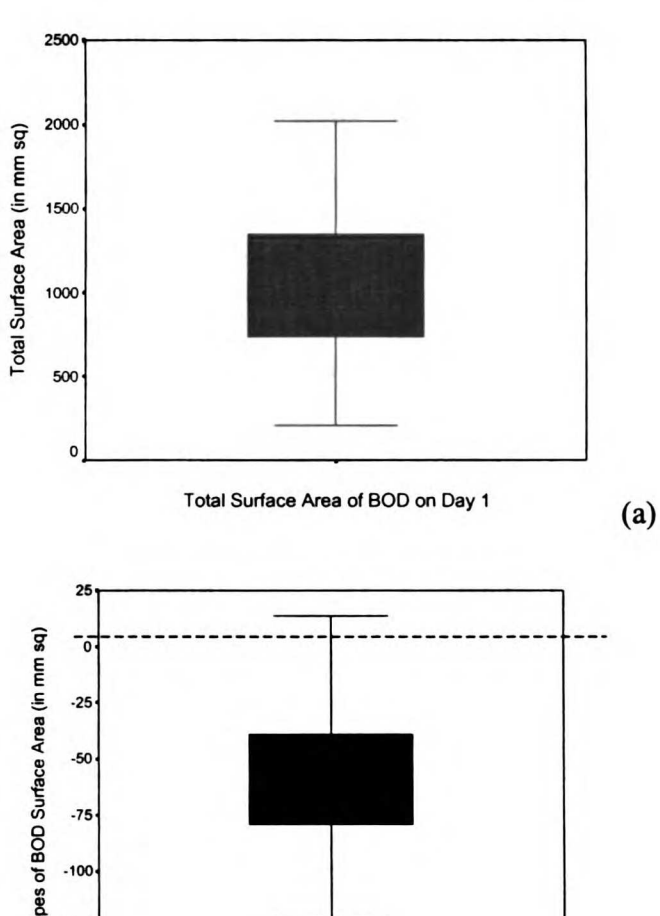


Figure 7. Total Surface Area on Day 1 (a) and Change in total surface area during hospitalization (b).

a) Shaded area represents 50% of Total Surface Area on Day 1. Lines outside shaded area represent upper 25% and lower 25% of Total Surface Area on Day 1. Line in shaded area represents median Total Surface Area on Day 1 (i.e. 50% of Total Surface Area are above and below median line).

b) Shaded area represents 50% of slopes of Total BOD surface area. Lines outside shaded area represent upper 25% and lower 25% of all slopes. Line in shaded area represents median slope of Total BOD surface area (i.e. 50% of slopes are above and below median line). β closer to 0 = no change in total surface area during hospitalization. $\beta < 0$ = decrease in total surface area during hospitalization. $\beta > 0$ = increase in total surface area during hospitalization.

Pain Quality. The total number of words selected on the word descriptor list of the APPT were counted for each day during hospitalization. On day 1, the mean number of word descriptors selected was 14, and on average 6 were sensory words, 2 were affective words, 3 were evaluative words, and 3 were temporal words. The most frequently selected words on day 1 are listed in Tables 3, 4, 5, and 6.

Table 3
Sensory Words (N=40)

	N	%
Pressure	28	70.0
Throbbing	27	67.5
Tight	27	67.5
Hurting	26	65.0
Aching	25	62.5

Table 4
Affective Words (N=40)

	N	%
Crying	27	67.5
Dizzy	26	65.0

Table 5
Evaluative Words (N=40)

	N	%
Uncomfortable	31	77.5
Uncontrollable	29	72.5
Never goes away	28	70.0
Annoying	24	60.0

Table 6
Temporal Words (N=40)

	N	%
Steady	27	67.5
Constant	27	67.5
Always	27	67.5
Continuous	25	62.5

As indicated in Figure 8, no significant changes were found in the total number of words selected during hospitalization, possibly due to the small number of words selected each day.

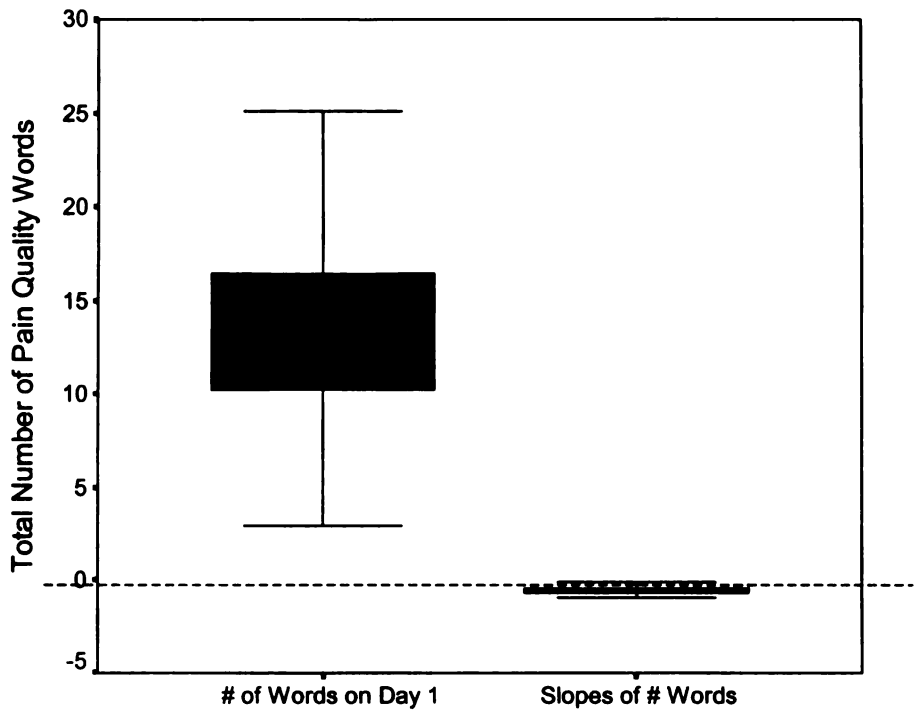


Figure 8. Total number of words selected on day 1 and change in the number of words selected during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line). β closer to 0 = no change in total number of words during hospitalization. $\beta < 0$ = decrease in total number of words during hospitalization. $\beta > 0$ = increase in total number of words during hospitalization.

Specific Aim 2. To describe changes in functional status (i.e., sleeping, eating, activity level) during hospitalization.

Amount of Sleeping. On day 1, the mean score on the NRS for the amount of sleeping at nighttime (i.e., 0=did not sleep at all to 10=slept a lot) was 4.45 ± 1.53 (range 1.99 to 8.68) and the mean score on the NRS for amount of sleeping during the day was 3.34 ± 1.53 (range .88 to 7.57). As illustrated in Figure 9, more than 75% of the patients perceived that they had little sleep on day 1.

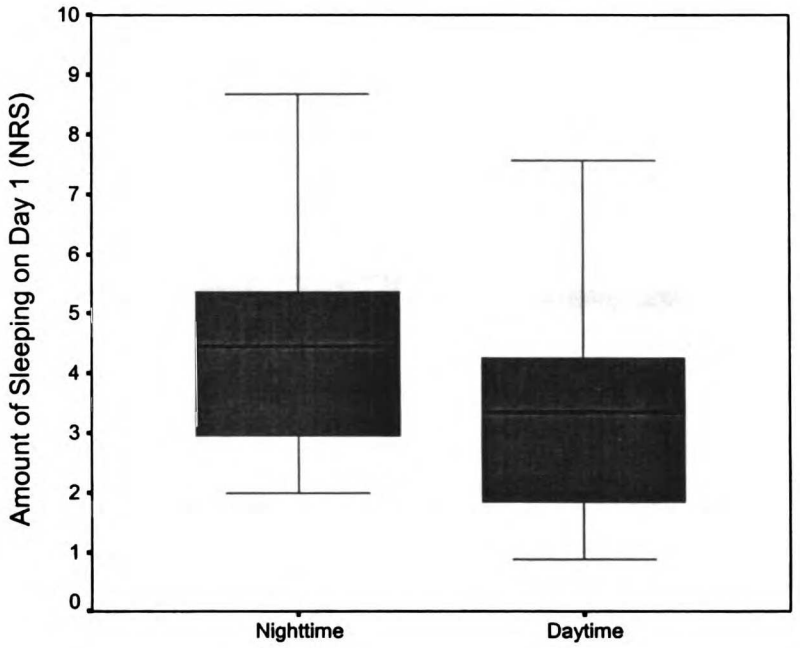


Figure 9. Amount of sleeping in the daytime and nighttime on day 1. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line).

Neither sleep score showed a significant amount of change during the hospitalization with a mean $\beta = .20 \pm .33$ (range $\beta = -.56$ to $\beta = .87$) for amount of sleeping during the night and a mean $\beta = -.14 \pm .34$ (range $\beta = -.91$ to $\beta = .52$) for amount of sleeping during the day (see Figure 10). These findings indicate that these children perceived that they had little sleep during the entire hospitalization.

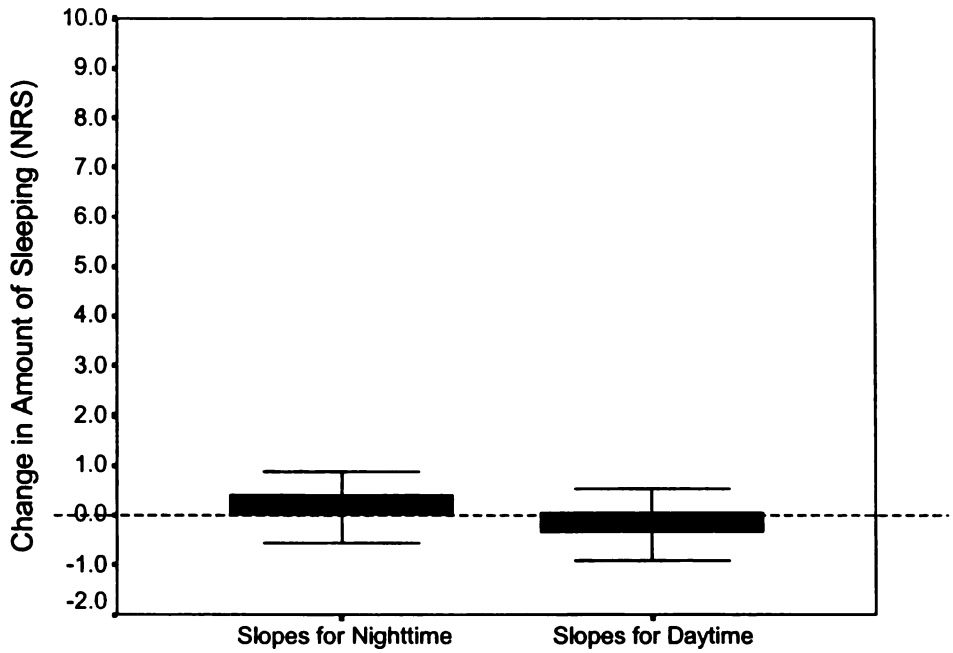


Figure 10. Change in amount of sleeping during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e., 50% of all scores are above and below median line). β closer to 0 = no change in amount of sleeping during hospitalization. $\beta < 0$ = decrease in amount of sleeping during hospitalization. $\beta > 0$ = increase in amount of sleeping during hospitalization.

Amount of Eating. On day 1, the mean score on the NRS for amount of eating (i.e., 0=did not eat anything to 10=ate a lot) was 2.55 ± 1.53 (range .09 to 6.78). This score did not show a significant change during the hospitalization with a mean $\beta = .19 \pm .34$ (range $\beta = -.58$ to $\beta = .85$). These findings indicated that the children perceived no change in food consumption during hospitalization (see Figure 11).

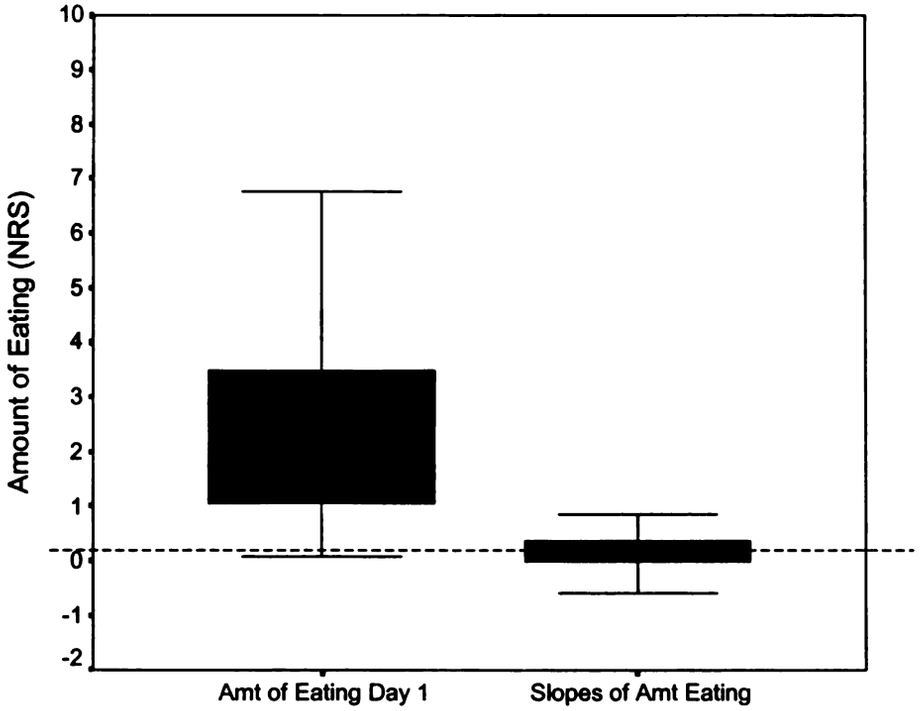


Figure 11. Average amount of eating on day 1 and change in amount of eating during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score. (i.e., 50% of all scores are above and below median line). β closer to 0 = no change in amount of eating during hospitalization. $\beta < 0$ = decrease in amount of eating during hospitalization. $\beta > 0$ = increase in amount of eating during hospitalization.

Amount of Activity. On day 1, the mean score on the NRS for amount of activity (i.e., 0=did not do anything to 10=did a lot) was 2.22 ± .79 (range .62 to 3.71). This score did not show a significant change during the hospitalization with a mean β = .33 ± .20 (range β= - .08 to β=.80). This finding indicated that the children perceive no change in activity during hospitalization (see Figure 12).

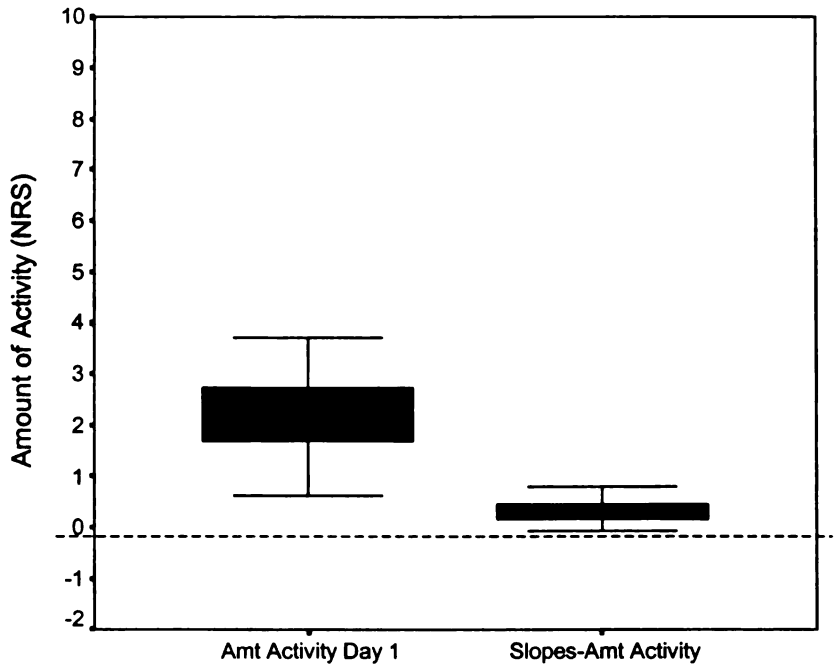


Figure 12. Average amount of activity on day 1 and change in amount of activity during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e., 50% of all scores are above and below median line). β closer to 0 = no change in amount of activity during hospitalization. β < 0 = decrease in amount of activity during hospitalization. β > 0 = increase in amount of activity during hospitalization.

Specific Aim 3. To describe changes in the presence or absence of selected signs and symptoms of vaso-occlusion during hospitalization.

The total number of signs and symptoms were counted from a list of 25 signs and symptoms associated with vaso-occlusion during hospitalization. The most common signs and symptoms reported on day 1 are listed in Table 7:

Table 7
Signs & Symptoms (N=40)

	N	%
Tired	20	50.0
Little or no appetite	19	47.5
Weak	18	45.0
Yellowing of the eyes	17	42.5
Coughing	16	40.0
Itching	14	35.0
Vomiting	10	25.0
Dizzy	10	25.0

The mean number of signs and symptoms reported on day 1 was 5.05 ± 1.22 (range 2.77 to 7.18). The number of signs and symptoms did not change during hospitalization with a mean β=.26 ± .24 (range β = -.15 to 1.08).

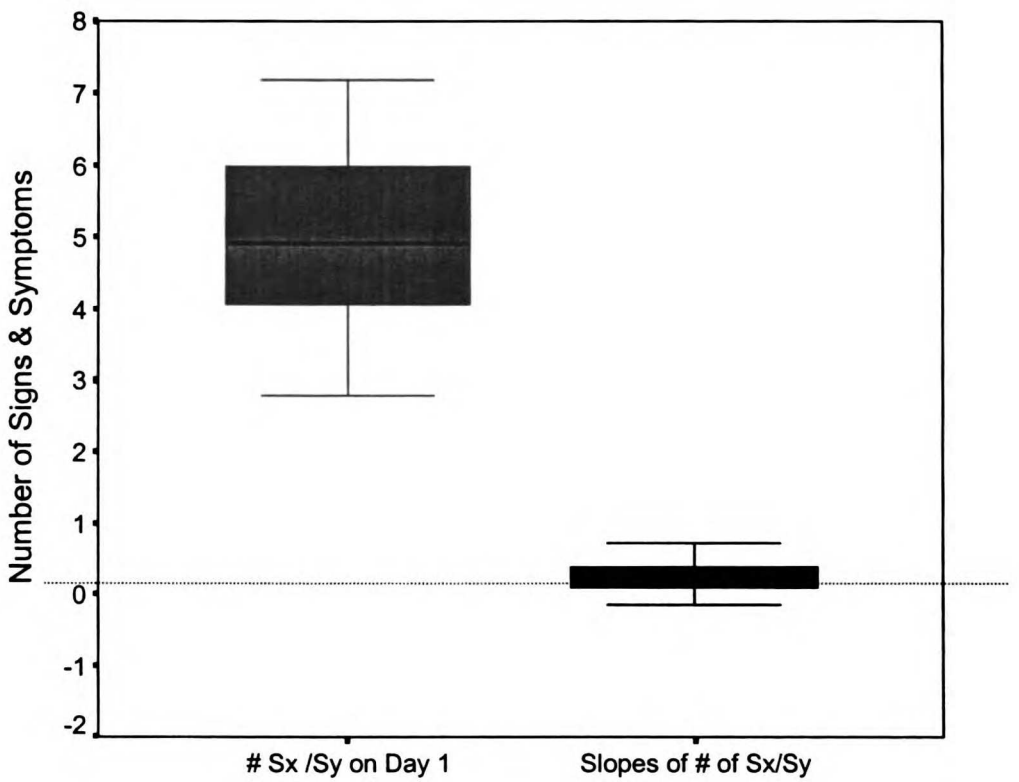


Figure 13. Number of signs and symptoms (sx/sy) on day 1 and change in number of signs and symptoms during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line). β closer to 0 = no change in total number of signs and symptoms (Sx/Sy) during hospitalization. $\beta < 0$ = decrease in total number of signs and symptoms during hospitalization. $\beta > 0$ = increase in total number of signs and symptoms during hospitalization.

Specific Aim 4. To describe changes in CBC values (i.e., red blood cell count, hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte count) during hospitalization.

CBC's were drawn once a day for children with sickle cell disease who were admitted to the hematology/oncology unit for vaso-occlusive pain.

Red Blood Cell (RBC) counts. One day 1, the mean RBC count (normal range: 4.2-5.6 million/microliter) was 2.92 mil/μL ± .79 (range 1.75 to 4.85). The RBC count did not change significantly during hospitalization with a mean β of -.02 ± .23 (range β = -.39 to β = .60), although graphically, there appears to be a downward trend in the count, which were stabilizing around day 4 to day 6.

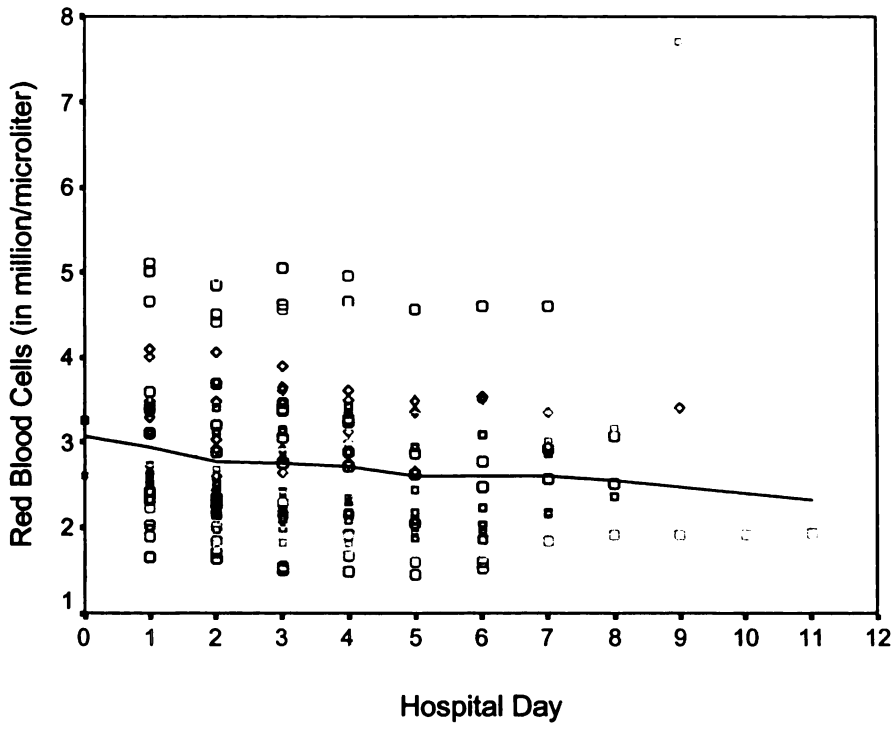


Figure 14. Changes in red blood counts during hospitalization.

Hemoglobin (Hgb). On day 1, the mean Hgb level (normal range: 13.3 – 16.6 gram/deciliter) was 8.93 gm/dL ± .3.81 (range 2.28 to 17.38). Hemoglobin levels did not change significantly during hospitalization with a mean β of -.12 ± .23 (range β = -.49 to β = .51), although graphically, there appears to be a downward trend in the levels, which were stabilizing around day 4 to day 6.

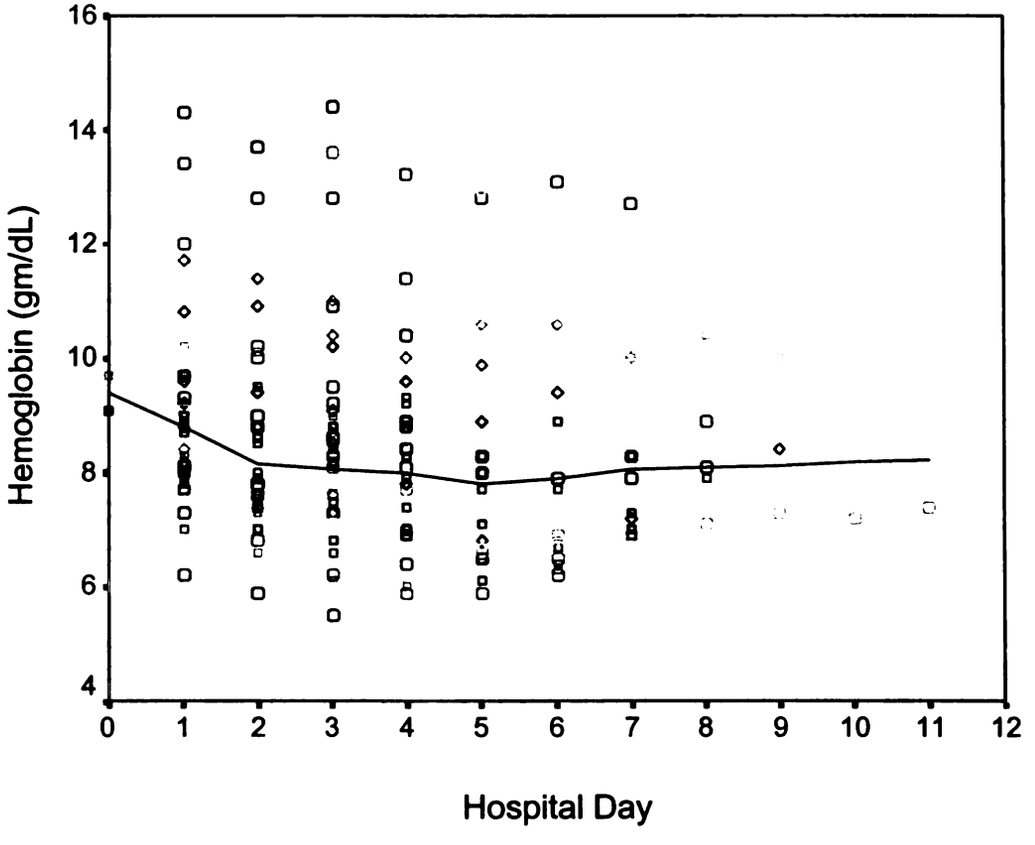


Figure 15. Changes in hemoglobin levels during hospitalization.

Hematocrit (Hct). On day 1, the mean Hct (normal range: 39.7 to 48%) was 25.67% ± .3.81 (range 19.02 to 34.12). The Hct did not change significantly during hospitalization with a mean β of -.30 ± .23 (range β = -.67 to β = .33), although graphically, there appears to be a downward trend in the values, which stabilize around day 4 to day 6.

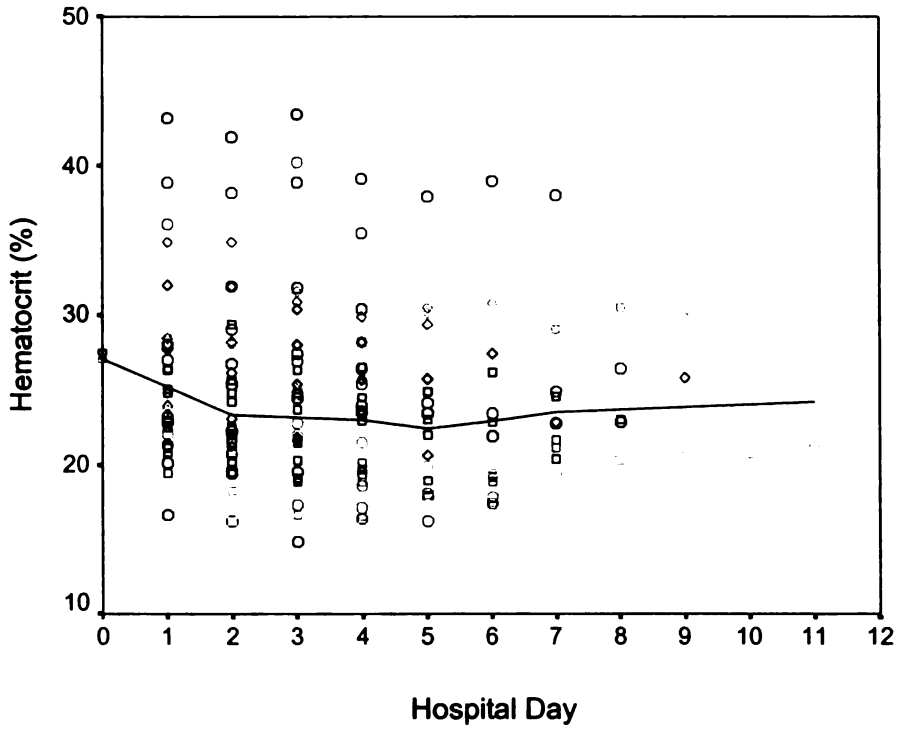


Figure 16. Changes in hematocrit values during hospitalization.

White Blood Cell Count (WBC). On day 1, the mean WBC count (normal range: 5.0 to 10.0 thousand/microliter) was 15.35 th/mcl ± .3.81 (range 8.70 to 23.80). The WBC count did not change significantly during hospitalization with a mean β of -.39 ± .23 (range β = -.76 to β = .24), although graphically, there appears to be a downward trend in the counts.

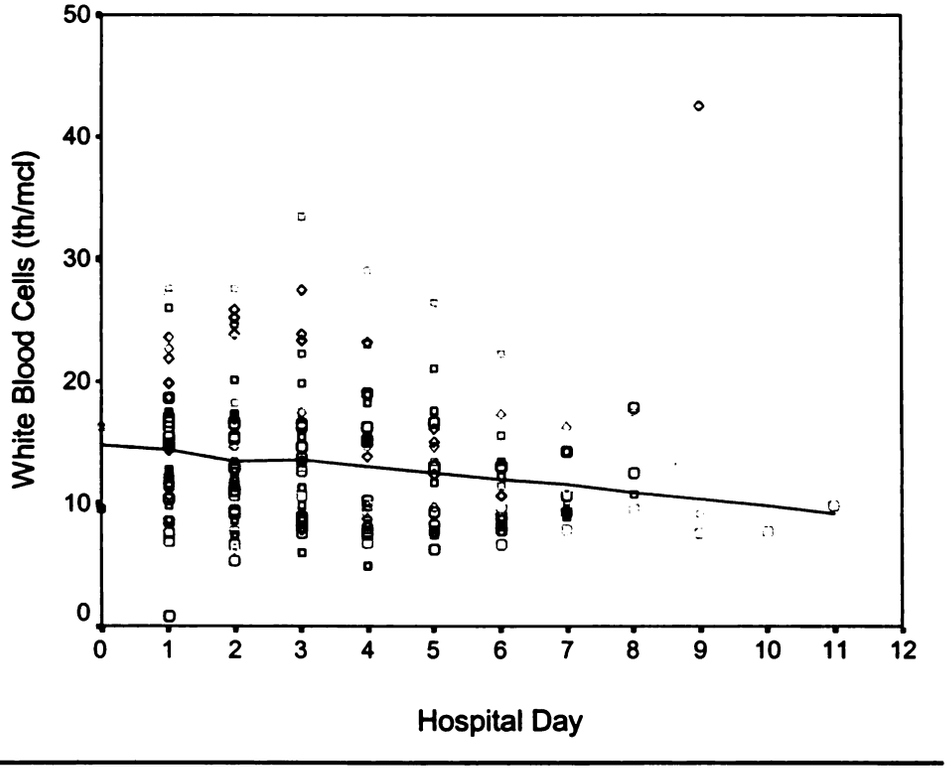


Figure 17. Changes in white blood cell counts during hospitalization.

Platelets (Plts). On day 1, the mean platelet count (normal range: 150 to 400 thousand/microliter) was 376.32 th/mcl ± .3.81 (range 369.67 to 384.77). The platelet count did not change significantly during hospitalization with a mean β of -.24 ± .23 (range β = -.61 to β = .39), although graphically, there appears to be an upward trend in the counts towards the end of hospitalization.

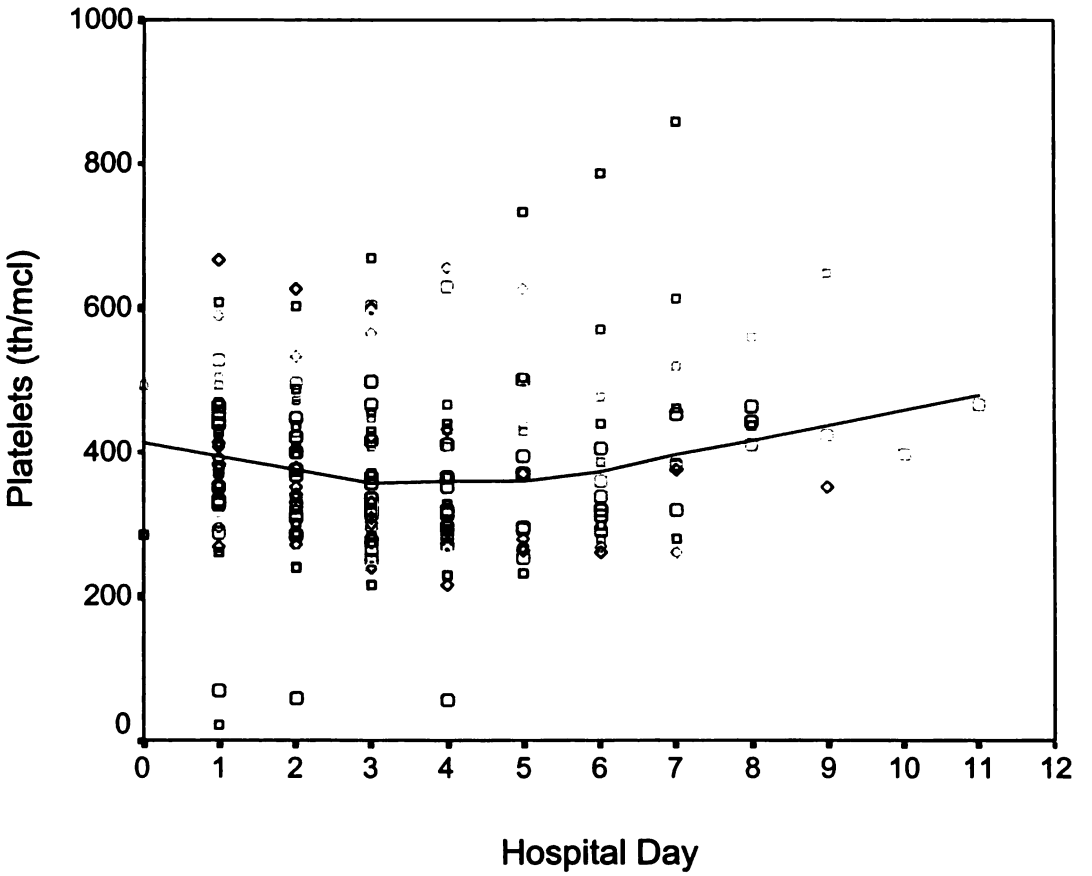


Figure 18. Changes in platelet counts during hospitalization.

Reticulocytes (retics). On day 1, the mean percentage of reticulocytes (normal range: 0.5 to 1.0%) was 11.23% ± 6.13 (range 3.23 to 26.35%). The percentages of reticulocytes did not change significantly during hospitalization with a mean β of .035 ± .99 (range β = -1.52 to β = 4.37), although graphically, there appears to be an upward trend towards the end of hospitalization.

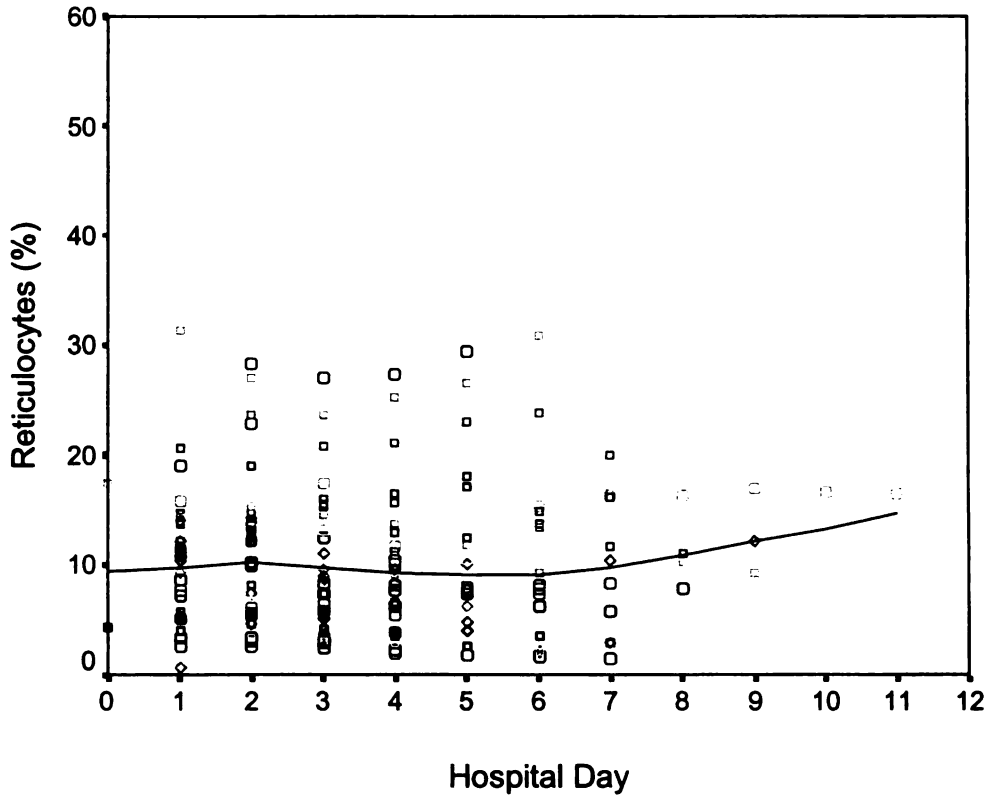


Figure 19. Changes in the percentages of reticulocytes during hospitalization.

Specific Aim 5. To describe the relationship between changes in pain intensity and changes in pain location surface area during hospitalization.

Using the slopes, Pearson Product Moment correlation (*r*) coefficients were calculated between changes in current pain intensity and changes in pain location surface area and between changes in worst pain intensity and changes in pain location surface area. A moderate positive correlation (r=.61, p=.000) was found between changes in current pain intensity and changes in pain location surface area, indicating that pain intensity and pain location surface area changed in the same direction. Figure 20 shows that the majority of the scores are in the lower quadrant ($\beta < 0$ for pain location surface area, $\beta < 0$ for current pain intensity), indicating that both slopes are negative. This finding suggests that as current pain intensity decreased during hospitalization, pain location surface area also decreased.

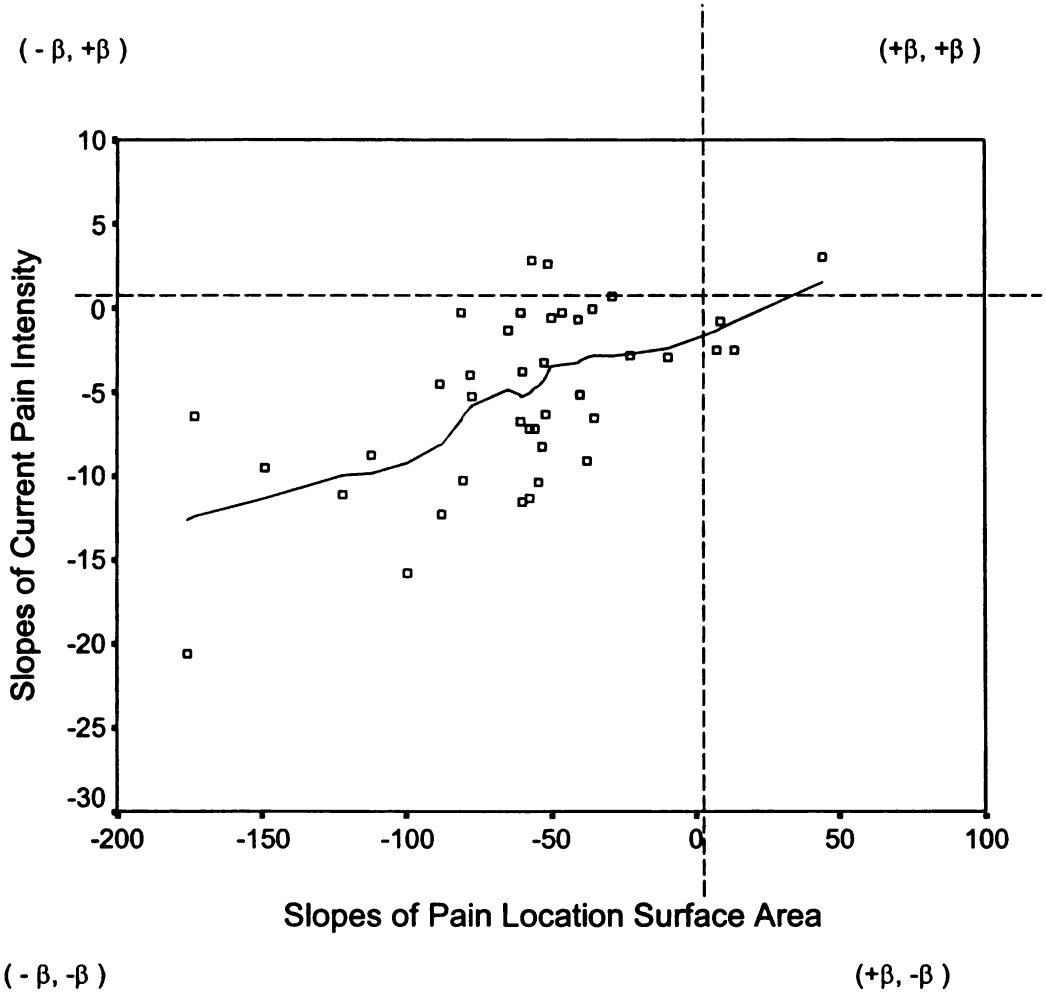


Figure 20. Relationship between changes in current pain intensity and pain location surface area (r=.604, p=.001). Y-axis represents amount of change in Oucher NRS. X-axis represents amount of change in surface area (mm^2). Both pain intensity (-β) and pain location surface area decreased (-β) for the majority of painful episodes. However, there were some painful episodes that were along the slope of 0 line, indicating no change in pain intensity, but to the left of the vertical 0 line, indicating decrease in pain location surface area.

A moderate positive correlation (r=.56, p=.000) was also found between changes in worst pain intensity and changes in pain location surface area, indicating that pain intensity and pain location surface area changed in the same direction. Figure 21 shows that the majority of the scores are in the lower quadrant ($\beta < 0$ for pain location surface area, $\beta < 0$ for current pain intensity), indicating that both slopes are negative. This finding suggests that as worst pain intensity decreased during hospitalization, pain location surface area also decreased.

As Figure 21 illustrates, there were slopes of some painful episodes that lie along the "0" horizontal line (indicating no change in pain intensity during hospitalization) and also lie along the "0" vertical line (indicating that the associated changes in pain location surface area also did not change during hospitalization). In addition, some pain intensity scores lie along the "0" horizontal line, indicating no change in pain intensity during hospitalization, but lie to the left of the "0" vertical line, indicating a decrease in pain location surface area.

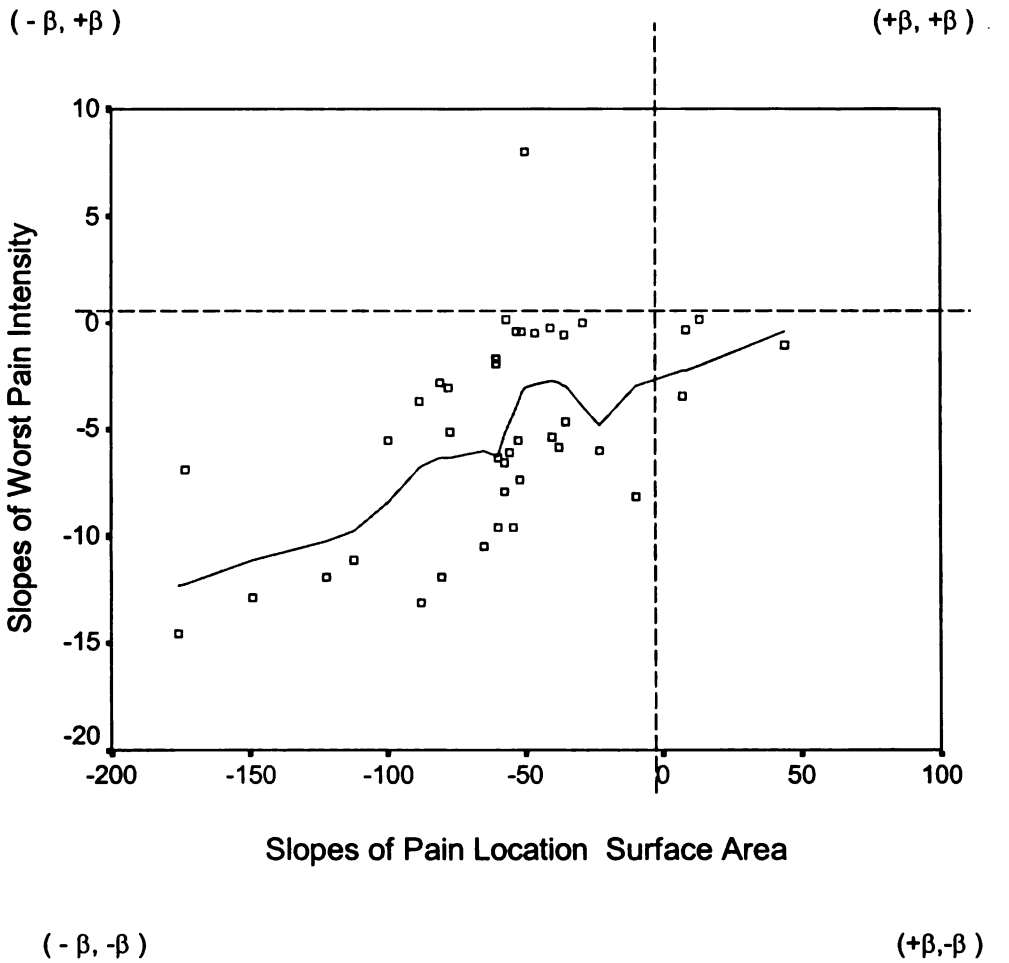


Figure 21. Relationship between changes in worst pain intensity and pain location surface area (r=.556, p=.000). Y-axis represents amount of change in Oucher NRS. X-axis represents amount of change in surface area (mm^2).

Specific Aim 6: To describe the relationships between changes in pain intensity and changes in the values of red blood cell count, hemoglobin, hematocrit, white blood cell count, platelet count, and reticulocyte count during hospitalization.

Using the slopes, Pearson Product Moment correlation (r) coefficients were calculated between changes in current pain intensity scores and changes in each of the CBC values, and between changes in worst pain intensity scores and changes in each of the CBC values.

Pain Intensity and RBC. No significant correlations ($r = .18$; $p=.265$) were found between changes in current pain intensity scores and changes in RBC values. No significant correlations ($r =.30$, $p =.061$) were found between changes in worst pain intensity scores and changes in RBC values (see Figure 22).

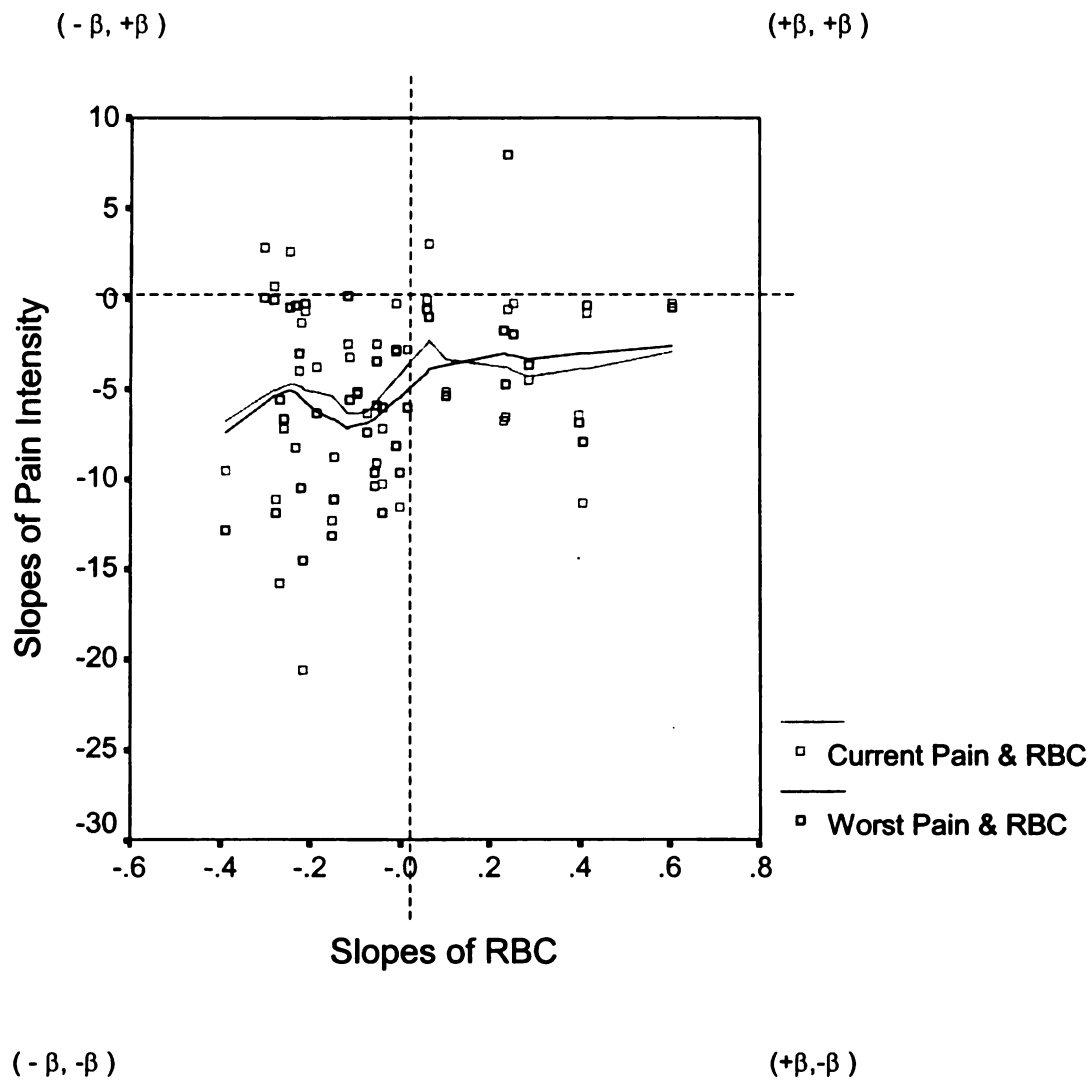


Figure 22. Relationship between changes in current and worst pain intensity scores and changes in red blood cell values.

Pain Intensity and Hgb. No significant correlations (r = .18; p=.265) were found between changes in current pain intensity scores and changes in Hgb values. No significant correlations (r =.30, p =.061) were found between changes in worst pain intensity scores and changes in Hgb values (see Figure 23).

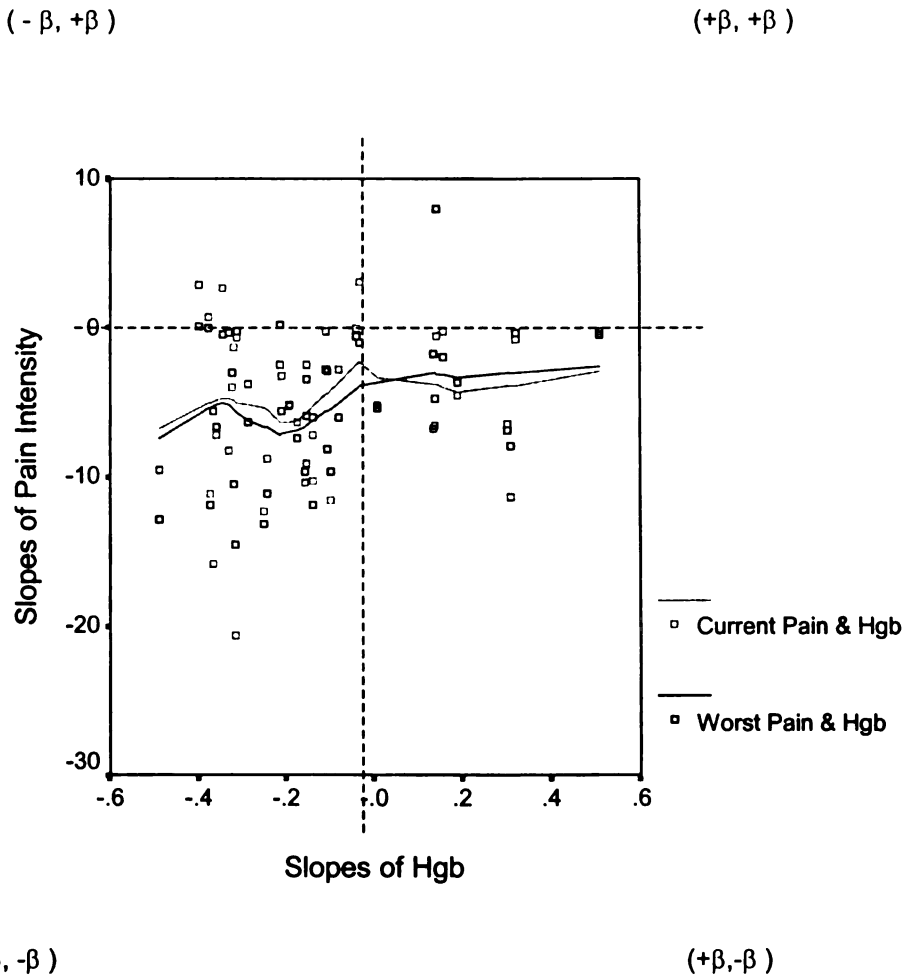


Figure 23. Relationship between changes in current and worst pain intensity scores and changes in hemoglobin values.

Pain Intensity and Hct. No significant correlations (r = .18; p=.265) were found between changes in current pain intensity scores and changes in Hct values. No significant correlations (r =.30, p =.061) were found between changes in worst pain intensity scores and changes in Hct values (see Figure 24).

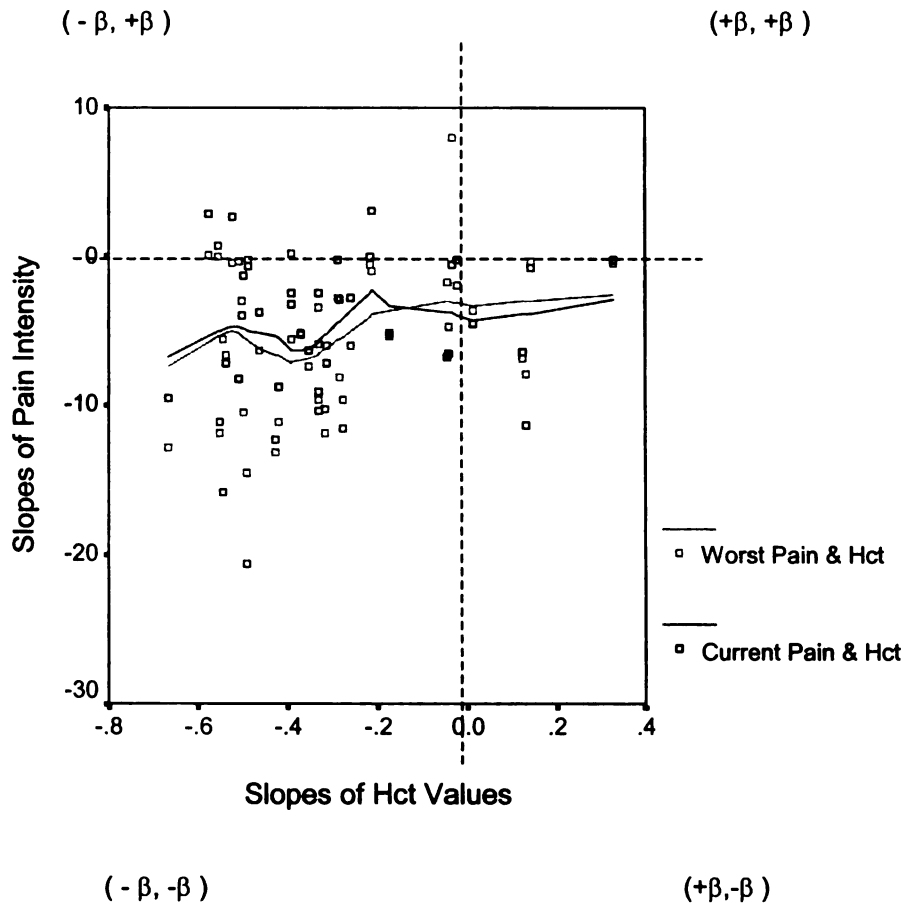


Figure 24. Relationship between changes in current and worst pain intensity scores and changes in hematocrit values.

Pain Intensity and WBC. No significant correlations (r = .18; p=.265) were found between changes in current pain intensity scores and changes in WBC values. No significant correlations (r =.30, p =.061) were found between changes in worst pain intensity scores and changes in WBC values (see Figure 25).

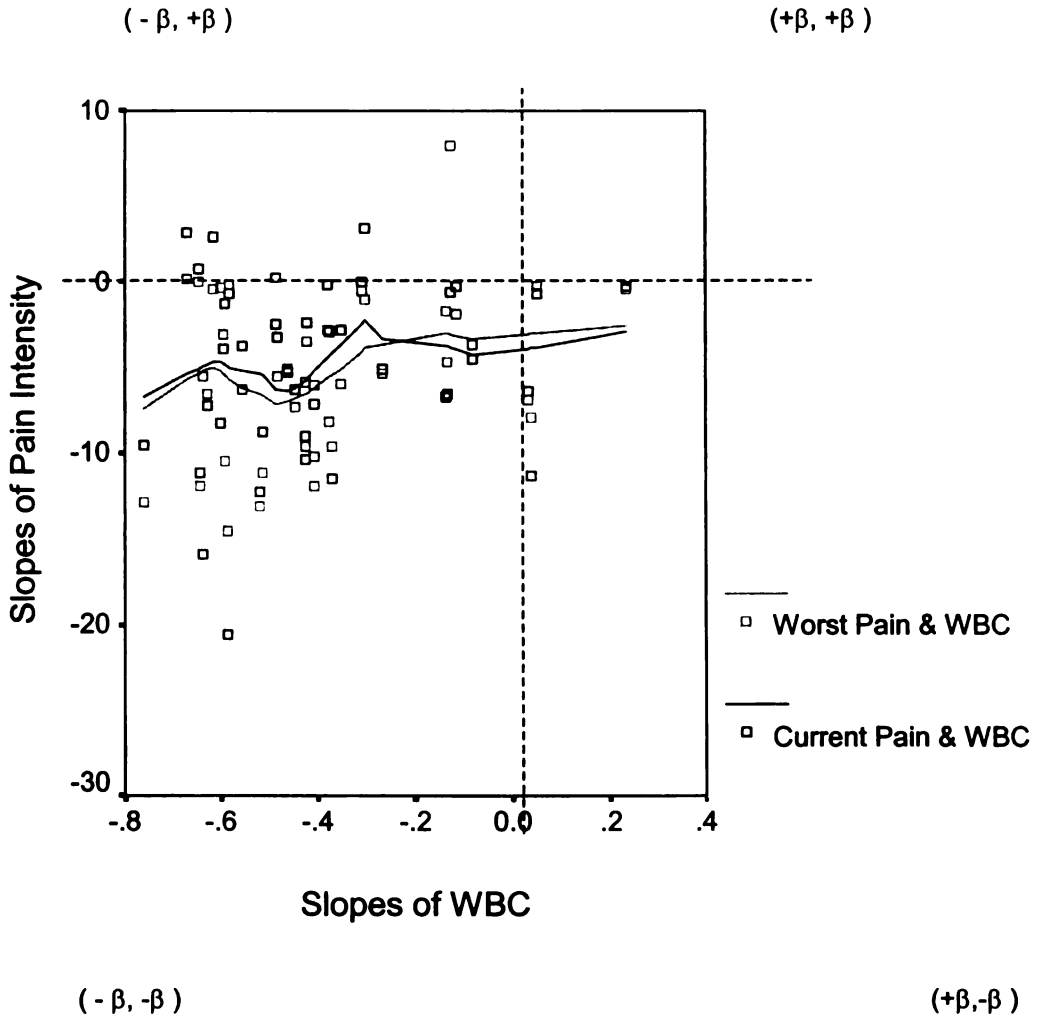


Figure 25. Relationship between changes in current and worst pain intensity scores and changes in white blood cell counts (WBC).

Pain Intensity and Platelets. No significant correlations (r = .18; p=.265) were found between changes in current pain intensity scores and changes in platelet counts. No significant correlations (r =.30, p =.061) were found between changes in worst pain intensity scores and changes in platelet counts (see Figure 26).

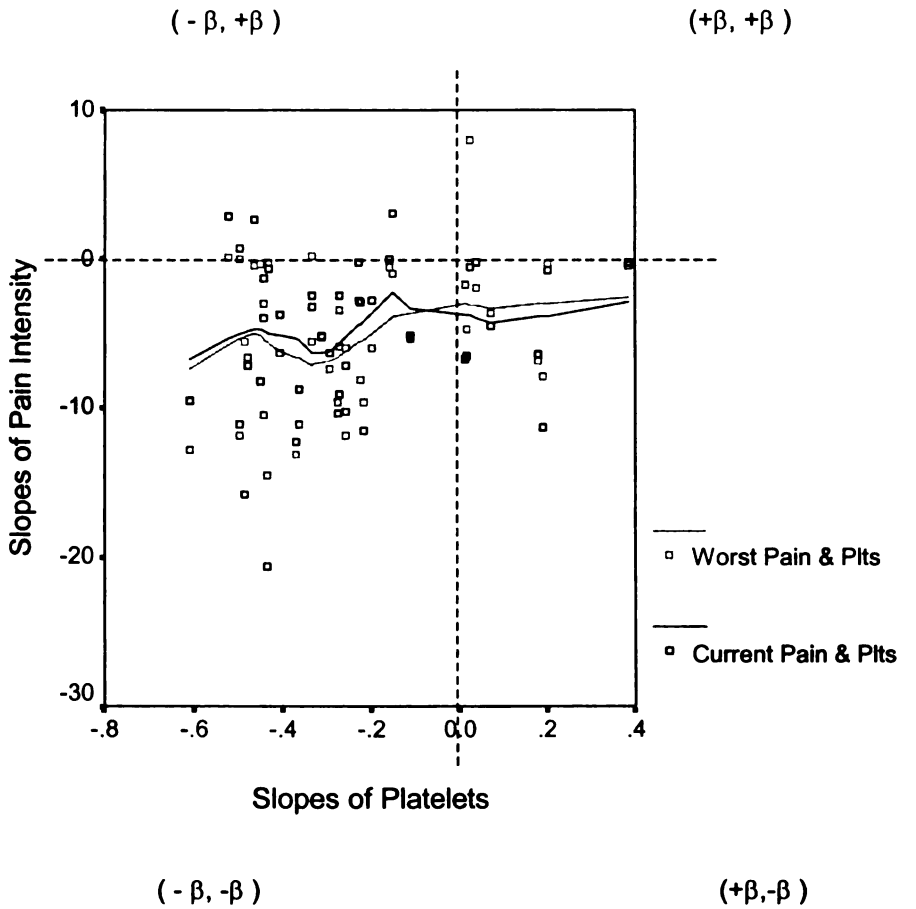


Figure 26. Relationship between changes in current and worst pain intensity scores and changes in platelet counts.

Pain Intensity and Reticulocytes. No significant correlations (r = .22; p=.18) were found between changes in current pain intensity scores and changes in reticulocyte values. No significant correlations (r = -.06, p =.709) were found between changes in worst pain intensity scores and changes in reticulocyte counts (see Figure 27).

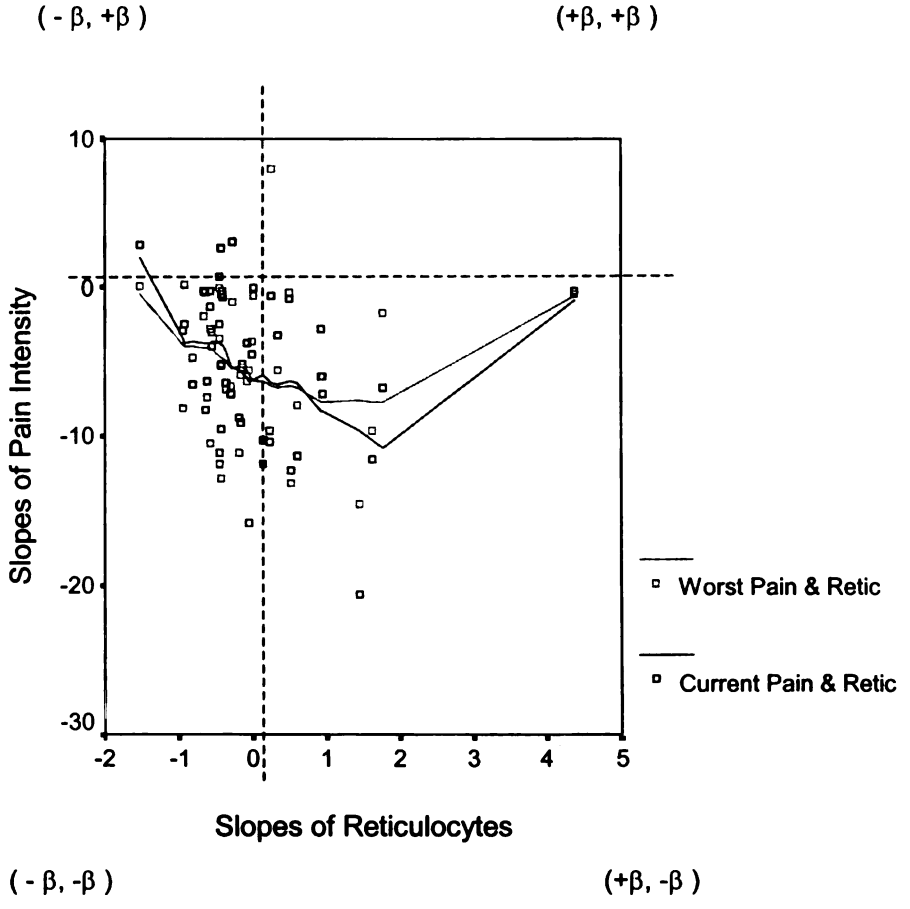


Figure 27. Relationship between changes in current and worst pain intensity scores and changes in reticulocyte counts.

Specific Aim 7. To describe changes in pharmacologic pain management strategies during hospitalization.

On day 1, PCA (patient controlled analgesia) morphine was prescribed for the majority of the painful episodes (n=35; 87.5%). The mean prescribed PCA dose was 1.69 mg/bolus (SD=.572 mg; range .3 to 3 mg), with a mean lockout interval of 11.14 minutes (SD=2.45 minutes; range 10 to 20 minutes). When compared with standard recommendations (Benjamin, 1999; Steedman, 1992; Taketomo, 2001, the PCA bolus doses were prescribed at low therapeutic, high therapeutic, and supratherapeutic levels, in 7.7%, 38.5%, and 43.6% of the episodes, respectively.

A basal rate was prescribed for the majority of the episodes (n=23; 65.7%) at a mean dose of 0.883 mg/hr (SD=.276; range 0.3 to 1.5 mg/hr). When compared with standard recommendations (Benjamin, 1999; Steedman, 1992; Taketomo, 2001), the basal rate was prescribed at subtherapeutic and low therapeutic levels in 5.2% and 53.8% of the episodes, respectively.

On day 1, the mean dose of morphine prescribed/24 hours was 132.67 ± 22.19 mg (range 102.67 to 201.42), which decreased significantly (β = -7.33 ± 1.91, $p < .0001$, range β = -3.91 to β = -12.37) during hospitalization. The mean dose of morphine administered/24 hours was 49.85 mg ± 22.19 (range 19.85 to 118.60), which decreased significantly (β = -5.66 ± 1.91, $p < .0001$, range β = -2.24 to β = -10.70) during hospitalization (see Figure 28 and 29). The mean dose of morphine administered per shift on day 1 were: 14.39 mg (SD=10.48; range 2 to 36.7 mg) on the day shift, 25.45 mg (SD=12.49; range .2 to 56 mg) on the evening shift, and 14.73 mg (SD=9.21; range 1 to 32.1 mg) on the night shift.

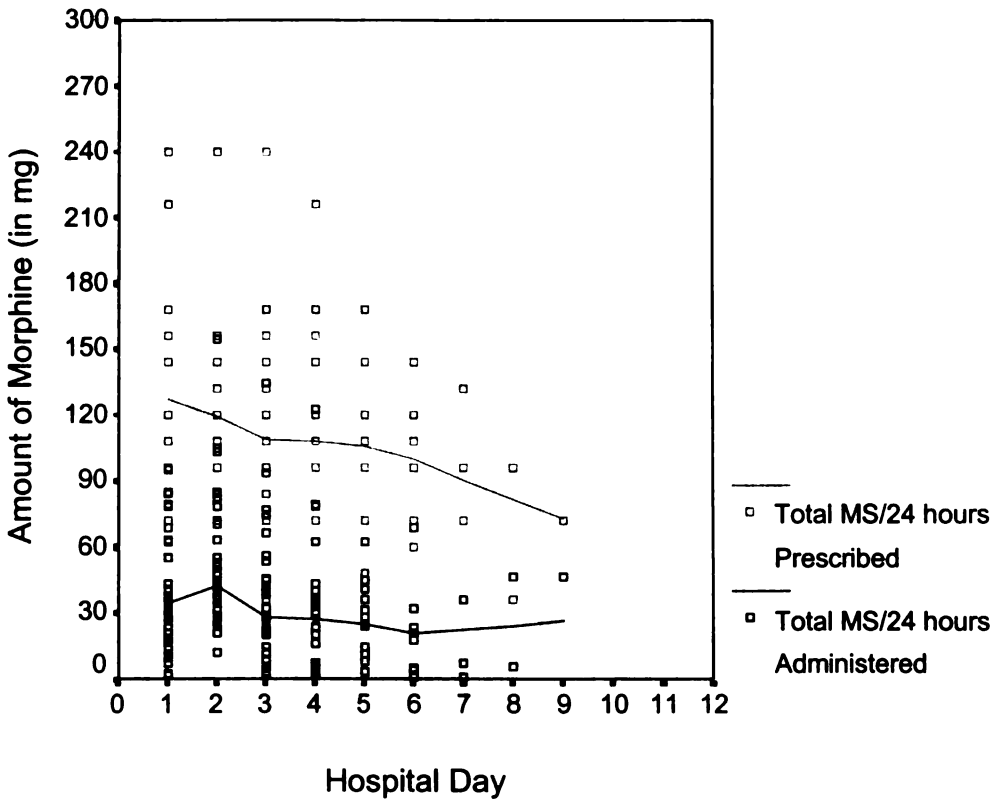
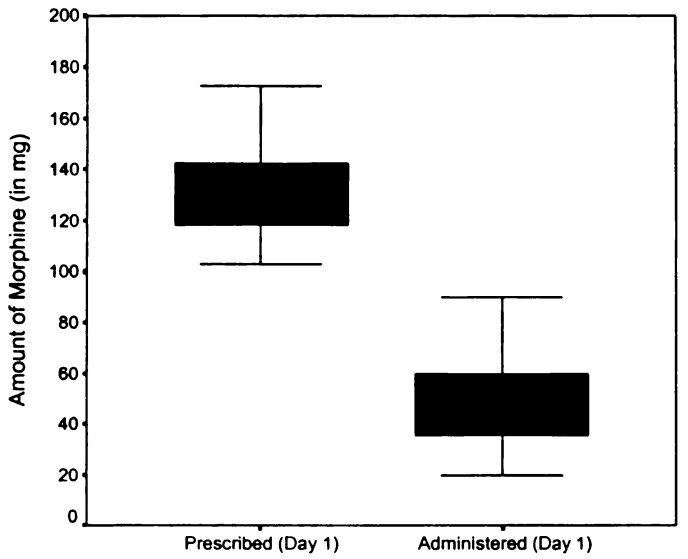
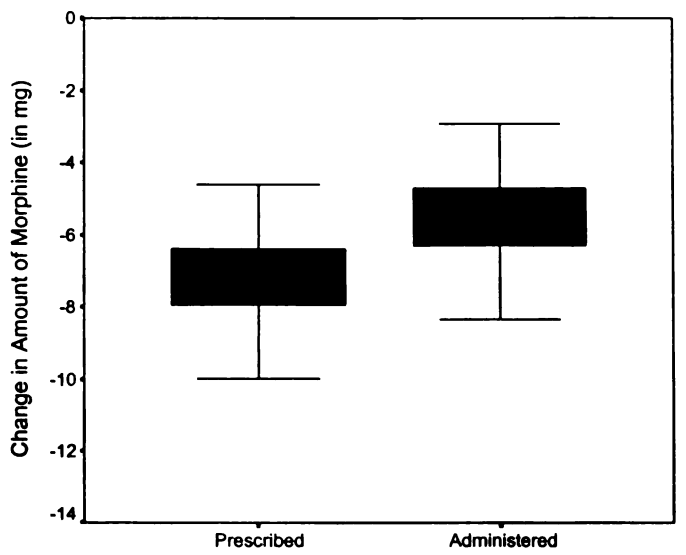


Figure 28. Changes in amount of prescribed and administered morphine/24 hours during hospitalization.



Day 1 (a)



Slopes (b)

Figure 29. Amount of morphine prescribed and administered on day 1(a) and changes in amount of morphine prescribed and administered during hospitalization (b). Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line). β closer to 0 = no change in amounts of morphine during hospitalization. $\beta < 0$ = decrease in amounts of morphine during hospitalization. $\beta > 0$ = increase in amounts of morphine during hospitalization.

On day 1, the percentage of morphine administered compared to what was prescribed was 35.02% (SD=22.19%, range 5.02 to 103.77%). The percentage of morphine administered versus prescribed did not show a significant change ($\beta = -.35 \pm 1.91$, $p = .61$, range –5.39 to 3.07) during hospitalization (see Figure 30).

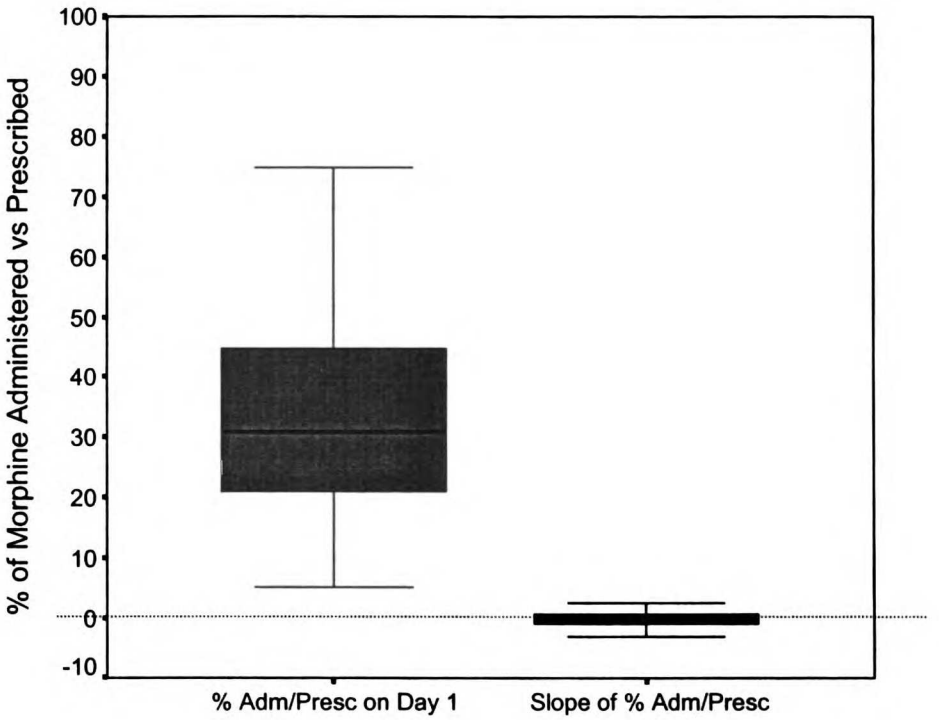


Figure 30. Percentage of morphine administered over prescribed and changes in the percentage of morphine administered over prescribed during hospitalization. Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line). β closer to 0 = no change in % of Administered/Prescribed MS during hospitalization. $\beta < 0$ = decrease in % of Administered/Prescribed MS during hospitalization. $\beta > 0$ = increase in % of Administered/Prescribed MS during hospitalization

Prescribed Medication Quantification Scale (MQS) Score. The mean MQS score prescribed on day 1 was 25.26 ± 5.11 (range 15.06 to 35.50), which decreased significantly (β = -1.47 ± .56, p <.0001; range -.45 to –2.90) during hospitalization. The mean MQS score administered on day 1 was 18.84 ± 3.59 (range 11.80 to 25.77), which decreased significantly (β = -1.18 ± .51, p <.0001; range –2.50 to 0.9) during hospitalization (see Figure 31).

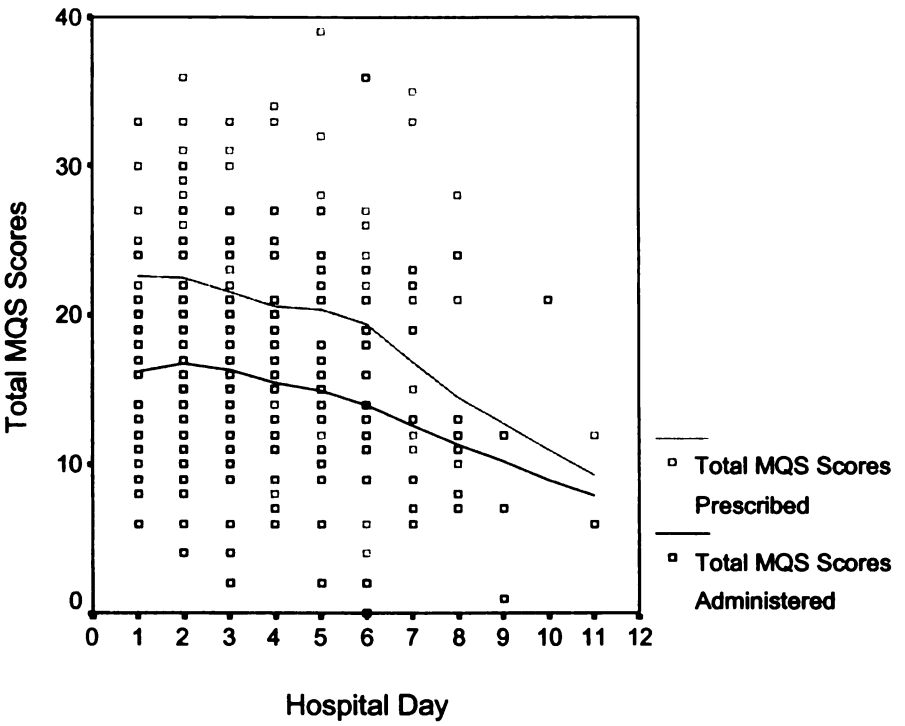


Figure 31. Changes in total MQS scores prescribed and administered during hospitalization.

Other Medications Administered for Pain Management. The majority of patients were also prescribed ketorolac and diphenhydramine on day 1.

Table 8

Co-Analgesics administered on day 1

	Frequency	Percent
Ketorolac	31	77.5
Diphenhydramine	21	52.5

Specific Aim 8: To describe the relationship between changes in children's self-reports of pain relief and changes in pharmacologic interventions during hospitalization.

Pain relief. A summary of the mean scores on the NRS for amount of pain relief from medications (0=did not help at all to 10=helped a lot) on day 1 is presented in Figure 32a, indicating that medications only "helped a little bit" during the day (mean = 3.90, SD = 1.53, range 1.43 to 8.13), during the night (mean = 3.30, SD = 1.53, range .84 to 7.53), and at the present time (mean = 3.63, SD = 1.53, range 1.16 to 7.86). These scores did not change significantly during hospitalization (see figure 32b).

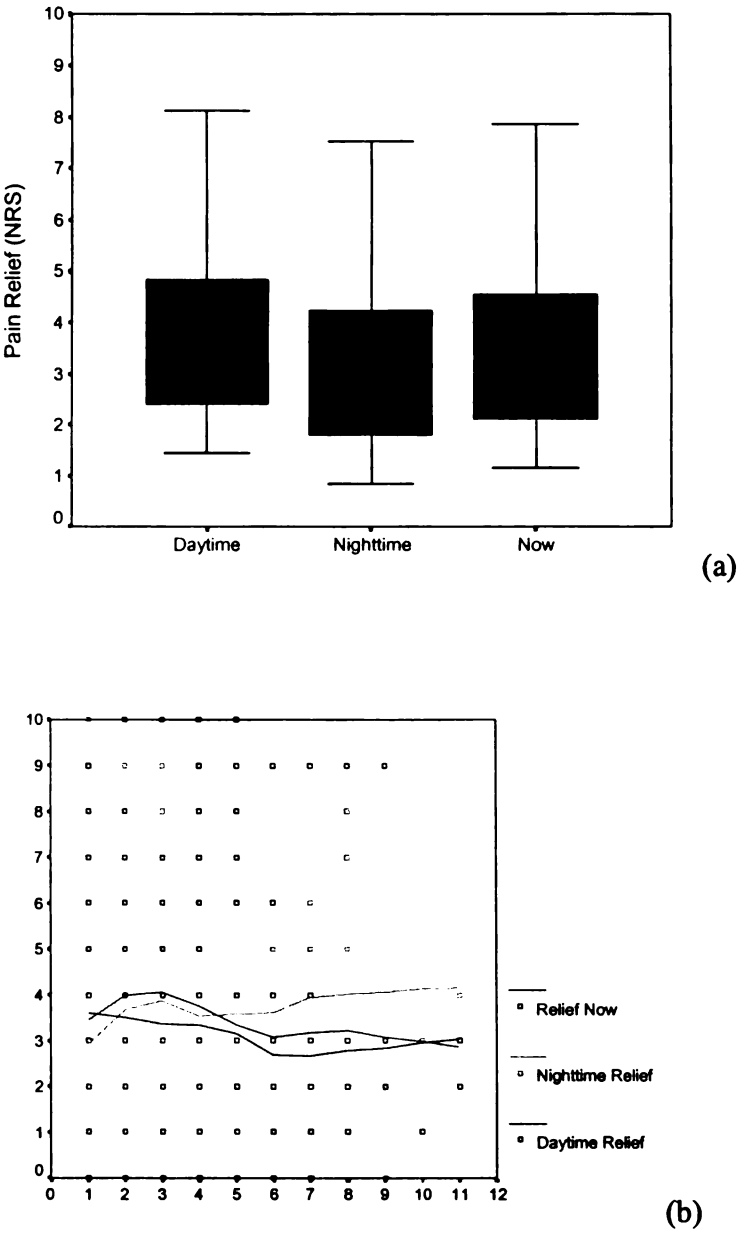


Figure 32. Amount of pain relief on day 1 (a) and change in the amount of pain relief during hospitalization (b).

a) Shaded area represents 50% of the scores. Lines outside shaded area represent upper 25% and lower 25% of all scores. Line in shaded area represents median score (i.e. 50% of all scores are above and below median line).

b) Slopes of Relief Now: Mean ß = .02, SD = .34, range -.75 to .68;
Slopes of Nighttime Relief: Mean ß = .21, SD = .34, range -.56 to .87;
Slopes of Daytime Relief: Mean ß = -.003, SD = -.003, range -.77 to .66.

As illustrated in Figure 33, no significant relationships were found between changes in amount of morphine administered/24 hours and changes in pain relief during the day (r=.085, p=.601), during the night (r=.085, p=.601), and pain relief now (r=.085, p=.601).

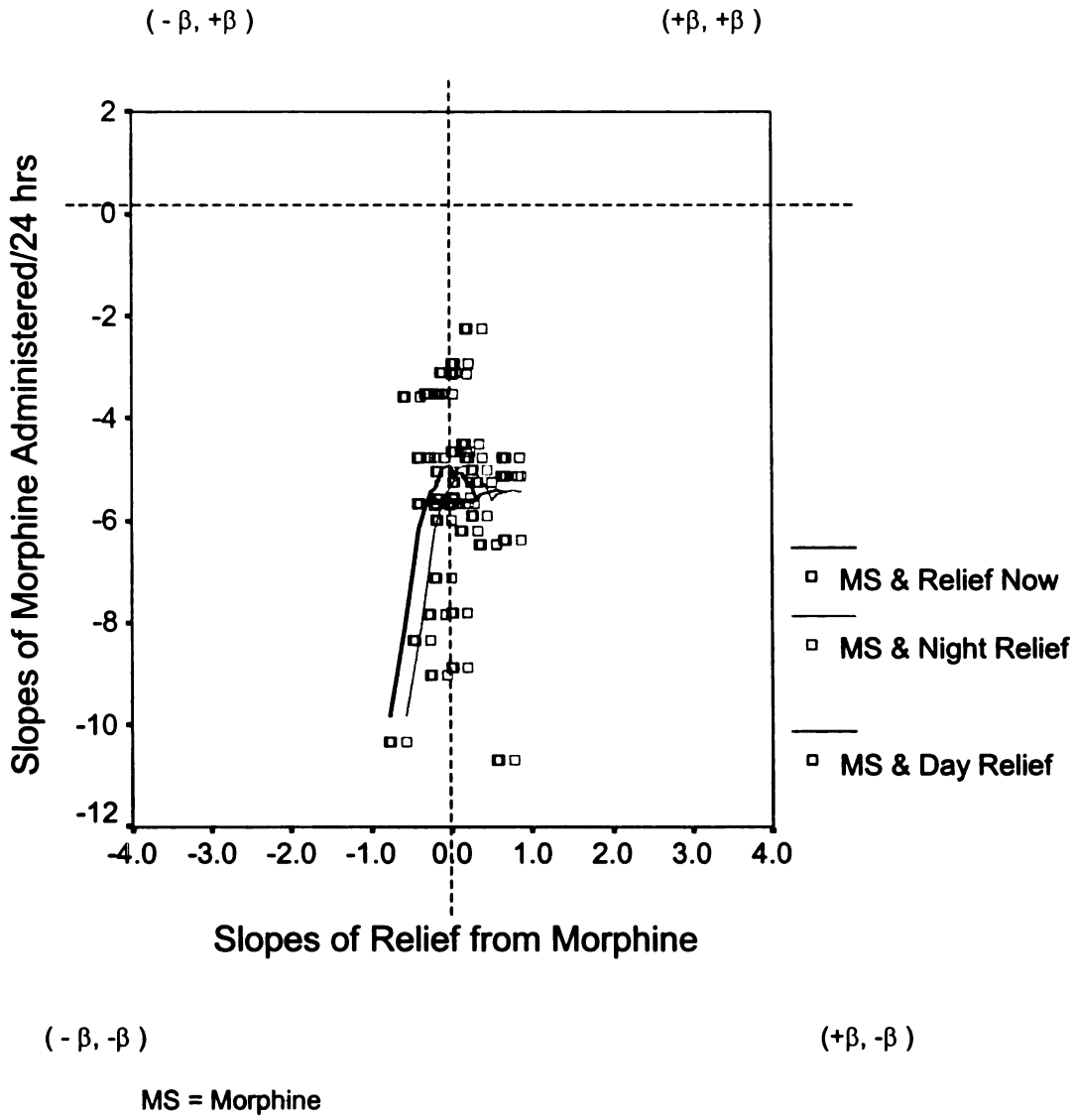


Figure 33. Relationship between changes in morphine administered/24 hrs and changes in pain relief during hospitalization.

As illustrated in Figure 34, no significant relationships were found between changes in the percentage of morphine dose administered versus prescribed and changes in pain relief during the day (r=.085, p=.601), during the night (r=.085, p=.601), and now (r=.085, p=.601).

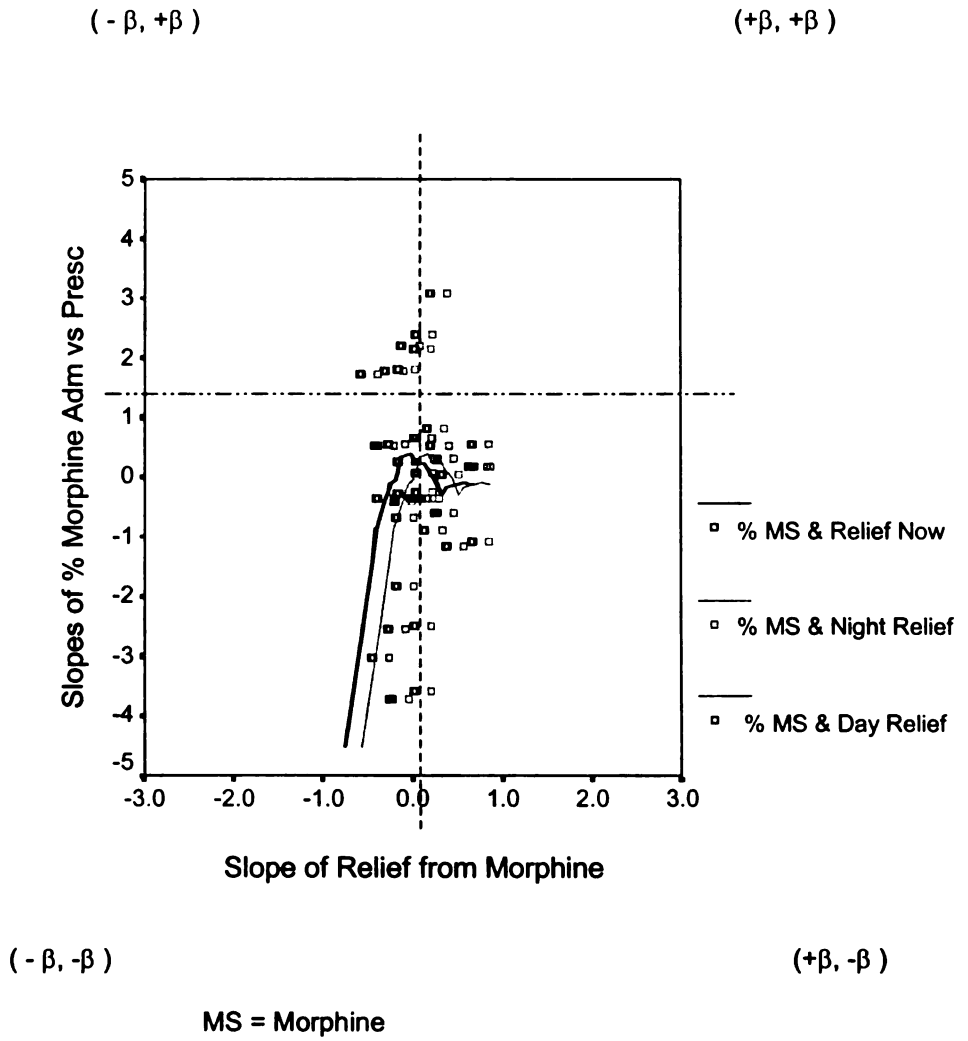


Figure 34. Relationship between changes in percentage of morphine administered versus prescribed and changes in pain relief during hospitalization.

Specific Aim 9. To describe the relationship between changes in three pain characteristics (i.e., intensity, location, quality) and pharmacologic interventions during hospitalization.

Pain Intensity and Pharmacologic Interventions. As illustrated in Figure 35, weak relationships were found between changes in current pain intensity and changes in MQS scores ($r = .320, p = .044$). No relationships were found between changes in current pain intensity and amount of morphine administered/24 hours ($r = .001, p = .997$), or between changes in current pain intensity and changes in the percentages of morphine administered versus prescribed ($r = .001, p = .997$).

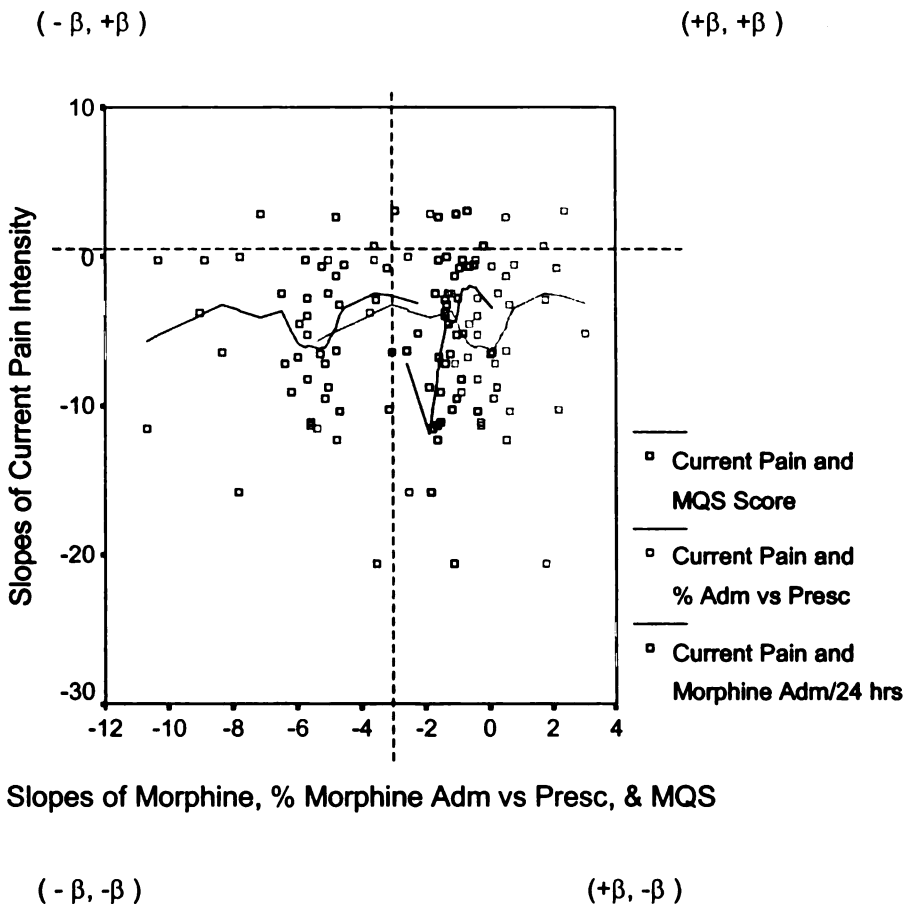


Figure 35. Relationships between current pain intensity and pharmacologic interventions.

As illustrated in Figure 36, weak relationships were found between changes in worst pain intensity and changes in MQS ($r = .308, p = .053$). No relationships were found between morphine dose administered/24 hours ($r = -.107, p = .512$) or between changes in worst pain intensity and changes in the percentages of morphine administered vs. prescribed ($r = -.107, p = .512$).

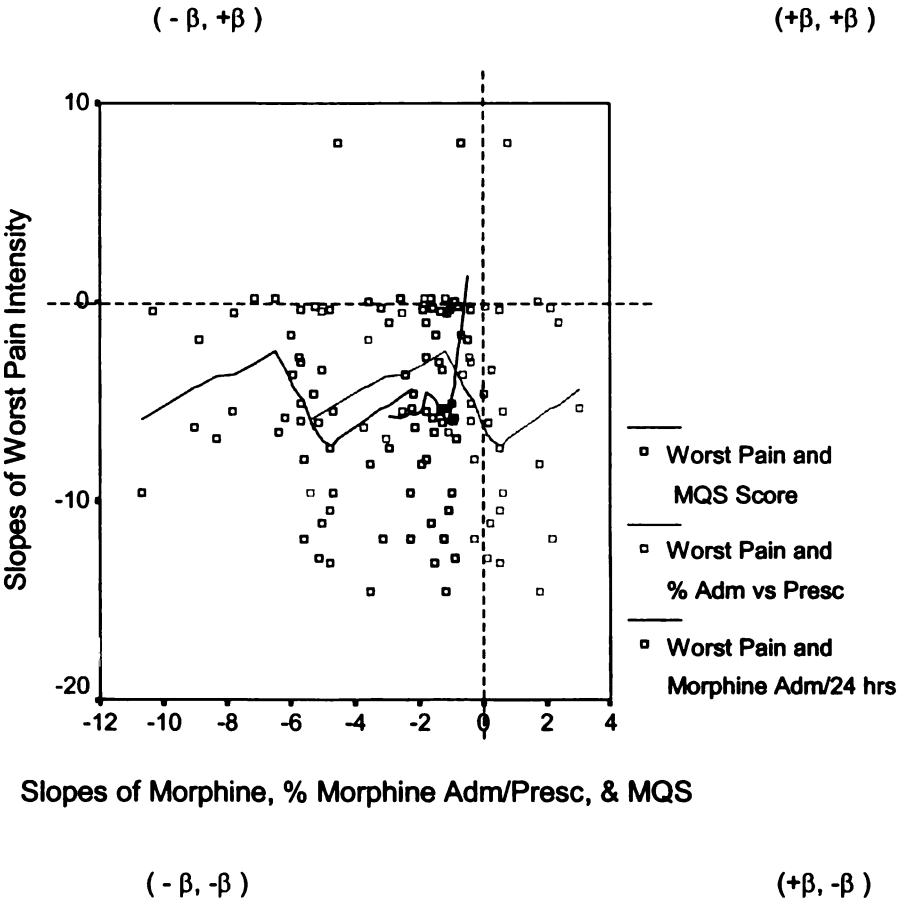


Figure 36. Relationships between worst pain intensity and pharmacologic interventions.

Pain Location and Pharmacologic Interventions. As illustrated in Figure 37, weak relationships were found between changes in the total number of body areas marked and changes in MQS scores ($r = .360, p = .023$). No relationships were found between changes in the total number of body areas marked and morphine dose administered/24 hours ($r = .072, p = .657$), or between changes in the total number of body areas marked and changes in the percentages of morphine administered vs. prescribed ($r = .072, p = .657$).

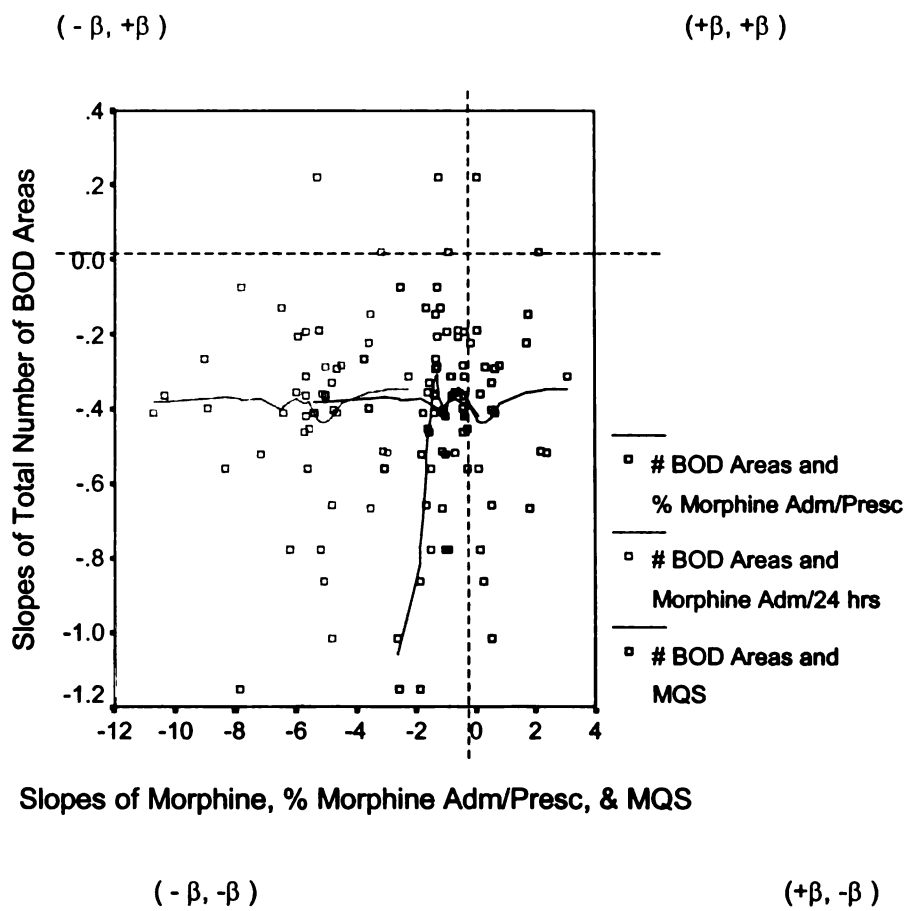


Figure 37. Relationships between total number of BOD areas and pharmacologic Interventions.

As illustrated in Figure 38, no relationships were found between changes in the total pain location surface areas marked and changes in: MQS scores ($r = .008$, $p = .961$), total morphine dose administered/24 hours ($r = .176$, $p = .277$), or the percentages of morphine administered vs. prescribed ($r = .176$, $p = .277$).

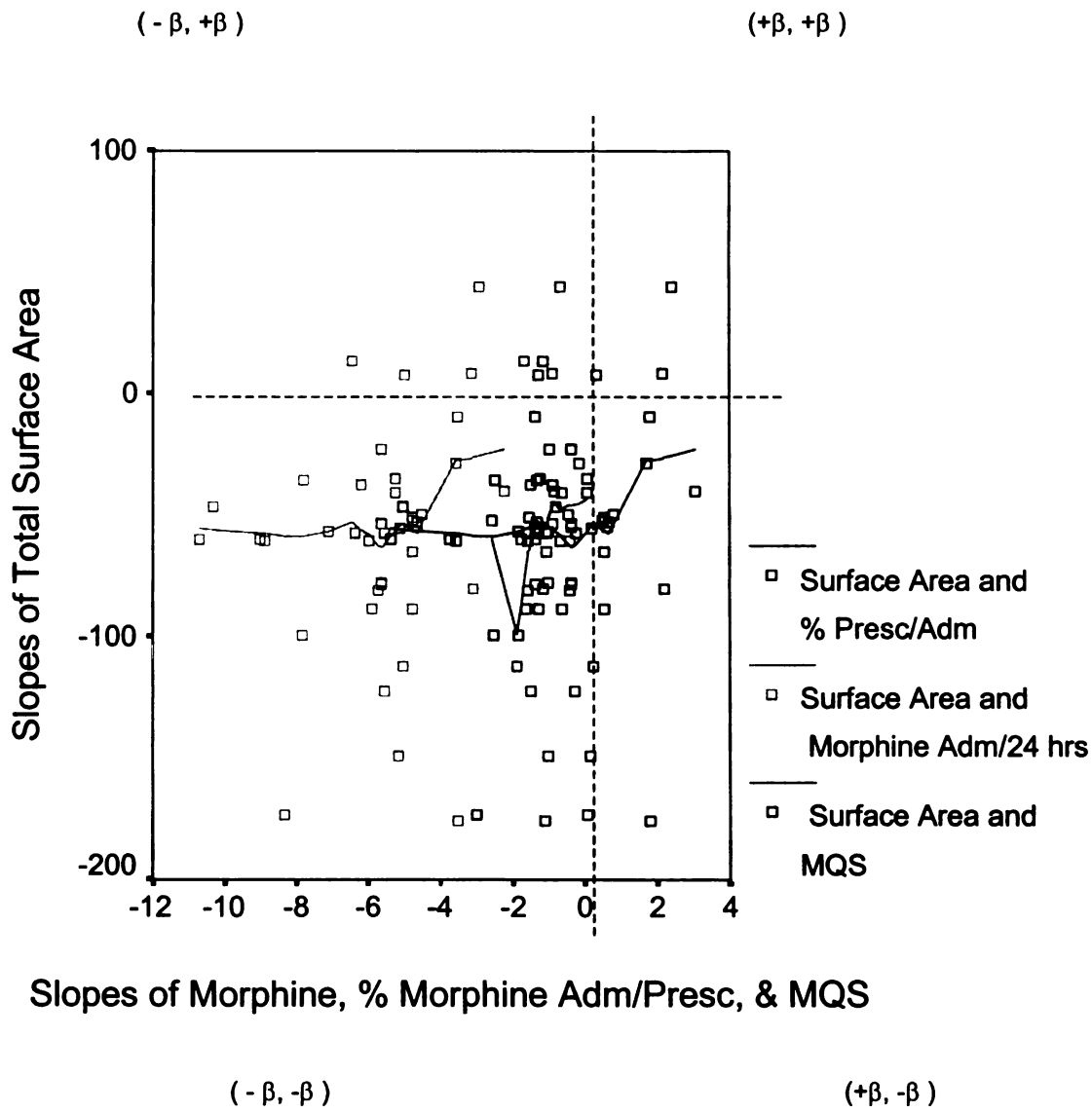


Figure 38. Relationships between total surface areas and pharmacologic interventions.

Pain Quality and Pharmacologic Interventions. As illustrated in Figure 39, no relationships were found between changes in the total number of word descriptors of pain quality and changes in: MQS scores (r = .284, p = .076), total morphine dose administered/24 hours (r =.110, p = .500), or the percentages of morphine administered versus prescribed (r =.110, p = .500).

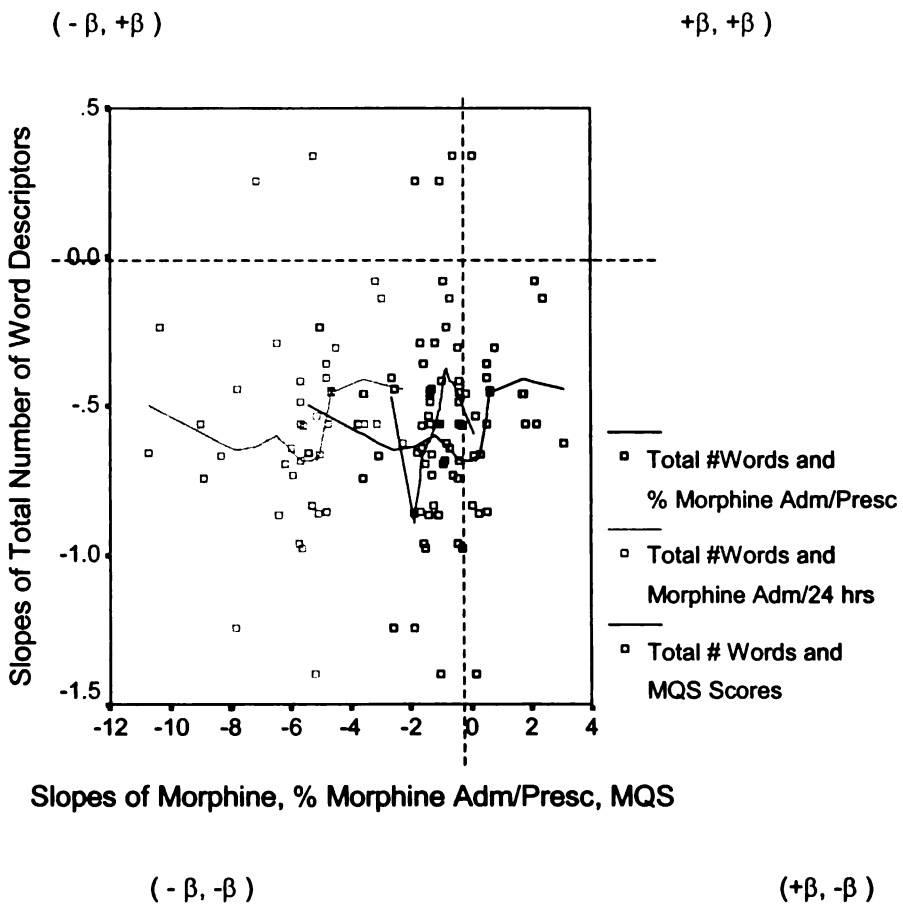


Figure 39. Relationships between total number of word descriptors and pharmacologic interventions.

CHAPTER 5

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

A longitudinal study that described the multidimensional aspects of pain in children with sickle cell disease who were hospitalized for painful vaso-occlusive episodes was conducted. Not only were changes in pain intensity, pain location, and pain quality evaluated from the day of admission through the day of discharge, but changes in functional status, such as sleeping, eating, and activity during hospitalization were also evaluated. In addition, clinical signs and symptoms associated with vaso-occlusive painful episodes and CBC values were examined in relation to the pain experience. Relationships between pharmacologic interventions and children's self-reports of pain relief, and between pharmacologic interventions and pain characteristics during hospitalization were also analyzed.

Discussion

Pain Intensity

This study showed that children had severe pain on day of admission with 50% of the episodes showing a current pain intensity score of >70 and a worst pain intensity score of > 80. A statistically significant decrease by a mean of 5% in current and worst pain intensity, and by a mean of 3% in least pain intensity scores was found during hospitalization. However, the magnitude of the change varied widely and the current, worst, and least pain intensity scores did not decrease in all episodes. In fact, in 25% of the episodes the current, worst, and least pain intensity scores did not decrease. Some episodes had an increase in current and least pain intensity of 3%, and and increase in worst pain intensity by 8%.

Walco and Dampier (1990) also examined the pain experience of hospitalized patients (n=12, ages 12 to 25 years) with sickle cell disease. They found that children were admitted with severe pain and that they reported a broad range of pain intensity scores. Their findings also showed a decrease in pain intensity scores over the course of hospitalization, with pain intensity ratings during hospital days 1 to 3 being significantly higher than during days 4 to 6 or 7 to 9.

Although the findings in the current study showed a statistically significant decrease in pain intensity by 5%, this change was not clinically significant. The APS Guideline for the Management of Pain in Sickle Cell Disease (1999) defines a clinically significant decrease in pain intensity as a 50% reduction from the upper end of the pain intensity scale. This guideline recommends that titration of analgesics be continued until a significant decrease in pain intensity for each individual is achieved, or until side effects become problematic.

The findings from this study showed that analgesics were not being titrated to decrease pain intensity ratings. Although the majority (82.5%) of the children were prescribed PCA morphine doses at high and supra therapeutic levels, the amount of morphine administered was relatively low compared to the prescribed amount. During hospitalization the average amount of morphine administered was only about 35% of the prescribed amount. Therefore, the lack of a clinically significant decrease in pain intensity may be due to children not self-administering the prescribed morphine. Health care providers may not have examined the self-reports of pain intensity in relationship to the amount of self-administered analgesics.

Pain Location

This study quantified two aspects of pain location, (i.e., the number of body areas and surface areas) marked on the BOD, which have not been examined previously in hospitalized children with sickle cell disease. The mean number of sites marked on the BOD was 8, which was consistent with a previous report (Franck, 2001), which compared characteristics of sickle cell disease pain in different settings, including the inpatient hospital setting. The most common painful sites marked in this study, as well as in the Franck study were the abdomen, chest, and back. Sporrer and colleagues (1994), however, noted that the most common painful sites reported by their sample of hospitalized children with sickle cell disease were "diffused" and involving not only the abdomen, chest, and back, but also the head, neck, and extremities. The differences in the sites marked may be due to the use of a body outline diagram in the current study, whereas Sporrer and colleauges collected data via self-report.

In contrast to the pain intensity ratings, which did not decrease in 25% of the episodes, the pain location surface area decreased in 100% of the episodes.
The small decrease in pain intensity ratings could be explained by the low amount of analgesic use. However, the large decrease in pain location surface area, despite the low amount of analgesic use is an interesting finding that requires further exploration. It is likely that the vaso-occlusive event was resolving as part of the natural evolution of the episode. Results of CBC values indicated that hemolysis (low RBC, low Hgb, low Hct, high reticulocyte counts) and inflammation (high WBC) were present at time of admission. The fact that the amount of pain location surface area or the spatial

distribution of the pain decreased significantly suggests that the hemolytic and inflammatory processes were resolving as time progressed.

An additional explanation for the large decrease in pain location surface area may be related to the effect of ketorolac. This study found that during the majority of the painful episodes (77.5%), children were administered ketorolac, a nonsteroidal anti-inflammatory drug. The decrease in pain location surface area may be related to the anti-inflammatory effect of ketorolac.

The most frequently used measure used for examining effectiveness of interventions is pain intensity. The measurement of pain location has not been used previously to determine the effectiveness of treatments. The current study shows that changes in number of body sites and changes in surface area over time decreased substantially, when pain intensity decreased only slightly. The measurement of pain location may offer another dimension for examining the effectiveness of treatments and monitoring the eventual progression of the vaso-occlusive episode.

Pain Quality

Children described the quality of the pain associated with sickle cell disease using sensory (pressure, throbbing, tight, hurting, aching), evaluative (uncomfortable, uncontrollable, never goes away, annoying), and affective (crying, dizzy) words. Only one previous report examined the sensory, evaluative and affective qualities of pain in hospitalized children with sickle cell disease (Walco and Dampier, 1990). In that study, three sensory words (beating, aching, and pounding), two affective words (tiring and sickening), and two evaluative words (uncomfortable and bad) were selected by 60% of the sample. In contrast to findings by Walco and Dampier (1990), where no temporal

words were chosen, children in the current study chose temporal words like steady, constant, always, and continuous, to describe the quality of their pain. Differences in the words most frequently selected is most likely due to the fact that this study used the word list from the APPT (Savedra, et al, 1994), while the Walco and Dampier study used the word list by Varni, Thompson, & Hanson (1987).

The mean total number of word descriptors selected in the Walco and Dampier study over the course of hospitalization was similar to the current study. In this study as well as in the Walco and Dampier study, the actual number of words decreased during the hospitalization. However, the amount of change was not statistically significant, which may be related to the fact that pain intensity did not decrease substantially. The selection of the words "uncontrollable and never goes away" may be reflective of the fact that pain intensity did not decrease substantially.

It is interesting to note that in this study, as well as in the Walco and Dampier study, the words did not appear to match high pain intensity ratings. For example, words from the word list, such as horrible and terrible from the evaluative group, screaming and terrifying from the affective group, or sharp and stabbing from the sensory group seem to connote more severe pain intensity, but these words were not selected by the majority of the patients. The constant, aching, and throbbing qualities of the reported pain suggests that the pain experienced by the children in this study is of the ischemic and inflammatory type of pain in the cutaneous, subcutaneous, and musculoskeletal tissues, as opposed to pain involving the central or peripheral nervous tissues, which would be described as shooting, burning, or shock-like sensations (Fields, 1987; Wall, 1994).

Functional Status

Children reported poor sleep during the night with a mean score of 4.45 on the 0 to 10 NRS, as well as during the day with a mean score of 3.34. The amount of sleep did not show a significant change during hospitalization. While there are no previous reports that examined the amount of sleeping in hospitalized children with a vaso-occlusive episode, data from the home and outpatient settings indicated that the quantity and quality of sleep were more likely to be disturbed on nights before and after vaso-occlusive pain days and that children reported poor sleep on an average of 43% of the days that they experienced pain (Shapiro et al., 1995). In another study (Walco & Dampier, 1990), pain was reported to interfere with sleeping and sleep duration was significantly less on nights when pain occurred.

Children in this study reported low activity scores during hospitalization, with a mean of 2.28 on the 0 to 10 NRS. The activity level did not change significantly during hospitalization. Previous reports from children, who were not hospitalized, indicated that they exhibited low activity levels when they experienced vaso-occlusive pain at home. Children did not attend school or go outside (Shapiro, Dinges, & Orne, 1990) and their parents reported that the painful episodes resulted in reductions in household activity, school activity, and social activity (Gil, Williams, Thompson, & Kinney, 1991). Parents also reported that pain interfered with favorite activities and sports (Walco & Dampier, 1990).

Children reported low eating scores, with a mean of 2.55 on the 0 to 10 NRS. No previous studies examined the eating patterns of hospitalized children with vaso-occlusive episodes.

Functional status in hospitalized children with sickle cell disease has not been evaluated previously during painful episodes. The findings from this study suggest that the pain experience interfered with functional status during hospitalization. Functional status is another dimension that needs to be examined when monitoring the effectiveness of treatments.

Signs and Symptoms Associated with Vaso-occlusive Painful Episodes

Parents and children reported signs and symptoms associated with VOE an average of 4 days prior to admission. About 4 signs and symptoms were reported with 85% of the children exhibiting general types of signs and symptoms such as tiredness, dizziness, weakness, yellowing of the eyes, and pallor. Gastrointestinal symptoms, such as nausea, vomiting, and change in appetite, were also reported, as well as respiratory (e.g., change in the way child breathes, sniffling, coughing) and musculosketal symptoms (e.g., swelling of hands/feet, tenderness, or stiffness in joints), and changes in skin color. In the current study, the onset of pain occurred a mean of 4.48 days prior to admission, which was simultaneous with the onset of other signs and symptoms associated with vaso-occlusion.

Previous reports (Akinola, Stevens, Franklin, Nash, & Stuart, 1992; Ballas, 1998; Ballas, 1995; Ballas & Smith, 1992; Beyer, Simmons, Woods, & Woods, 1999), also noted symptoms occurring within approximately three days prior to admission, such as paleness in fingernails, numbness, aches, and parasthesia in the sites subsequently affected by pain (Ballas, 1995). In the report by Murray and May (1988), patients were noted to have experienced symptoms that occurred up to 24 hours before developing features typical of the episode, such as numbness, aches, and pins and needles sensations

in the areas subsequently affected. Beyer, Simmons, Woods, and Woods (1999), also reported that, parents and children were able to note signs and symptoms such as change in the color of the eyes (loss of usual appearance, or luster, a yellowish hue in the sclera, darkness around the eyes) and pallor around the mouth.

While the actual number of signs and symptoms decreased each day, the amount of change was not statistically significant. It should be noted that only the presence or absence of the signs and symptoms were observed. The severity of the symptoms or the qualitative change in the signs and symptoms were not evaluated. Although some signs and symptoms such as fever, changes in breathing pattern, and vomiting may have resolved, other signs and symptoms, such as yellowing of the eyes, swelling of the hands and feet, and tenderness and stiffness in joints did not stop abruptly or disappear entirely, but gradually waned and may still be present during the day of discharge.

Although the signs and symptoms were noted at the same time that pain was present, it is not possible to differentiate whether they were related to the physiological processes related to pain or the underlying pathology. The signs and symptoms such as yellowing of the eyes, swelling of the hands and feet, and tenderness and stiffness in joints, were more reflective of the pathology, rather than the pain experience (Ballas, 1995).

CBC Values and Pain Intensity

At the time of admission, children presented with lower than normal RBC count (2.92 mil/μL), Hgb (8.93 gm/dL), and Hct (25.67%) values and a higher than normal reticulocyte count (11.23%), indicating that hemolysis was evident (Ballas, 1998; Ballas, 1995). Although these values did not show a statistically significant change during

hospitalization, RBC, Hgb, and Hct had a downward trend initially, and then stabilized or returned to baseline levels after 4 to 6 days. The reticulocytes count also did not change significantly during hospitalization, but showed an increasing trend between days 4 to 6. The change in pain intensity scores appeared to parallel these changes, when there was a slow downward trend until day 4 to 6, and remained steady after day 6. The mean length of stay in this study was 5.86 days, which appeared to coincide with the days when the stabilization of pain and hemolysis may be occurring.

The children also presented with slightly higher than normal WBC values (15.35 th/mcl), indicating that an inflammatory process (Ballas, 1998; Ballas, 1995) was evident at the time of admission. The WBC count did not show a statistically significant change during hospitalization. However, the WBC count showed a decreasing trend initially and then returned to approximately normal levels by day 4 and 5, again, possibly indicating stabilization of pain and inflammation. The platelet count did not change during hospitalization, but it showed an increasing trend after day 4 to day 6, which may indicate rebound thrombocytosis (increased platelets) that was previously reported by Ballas (1995; 1998). The increase in platelets may be related to the inflammatory mediators that include platelet activating factors that cause the local release of other mediators from white blood cells and attract other white cells to the site of inflammation (Colditz, 19991; Levine & Reichling, 1994). The return of WBC's to normal levels and the occurrence of a rebound thrombocytosis on days 4 to 6 appear to coincide with the days when pain was more steady and hemolysis was resolving. Therefore, CBC values may offer another dimension for monitoring the eventual progression of the vaso-occlusive episode.

Pharmacologic Interventions

The findings in this study showed that the children were not using the analgesics that were prescribed during hospitalization. Morphine administered via patient controlled analgesia (PCA) was prescribed for the majority of the episodes (87.5%). PCA doses at a mean of 1.69 mg/dose were prescribed at high and supra therapeutic levels in 82% of the episodes. Basal rates at a mean of 0.88 mg/hr were prescribed at sub therapeutic and low therapeutic levels in 59% of the episodes.

An interesting finding from this study is that children self-administered only 35% of opioids that were prescribed, considering that they were reporting high pain intensity scores during hospitalization. In 100% of the episodes, the administered amount of morphine was 65% lower than the prescribed amount. The report by Shapiro and colleagues (Shapiro & Cohen, 1993) also noted that patients in their sample received only 37% of the allowed dose on the day of maximum use.

The low self-administered use of opioids in relation to the prescribed amount is contrary to the beliefs of health care providers who hold sterotypic attitudes and stigmatize patients with sickle cell disease as addicts and drug seekers (Alleyne & Thomas, 1994; Armstrong, Pegelow, Gonzales, & Martinez; Ballas, 1996; Gorman, 1999; Maxwell, Streetly, & Bevan, 1999; Pegelow, 1992). Schechter and colleagues (Schechter, Berrien, & Katz, 1988) also noted that despite easy access to an opioid drug, the children used opioids only when their pain was intolerable, and reduced this usage as their painful episode subsided. These findings suggest that the fears and concerns for psychological dependence or addiction in children with sickle cell disease are unwarranted.

The prescribed PCA regimen in this study with low basal rates (mean rate at .015 mg/kg/hr), low PCA doses (mean PCA dose at .029 mg/kg/dose), and a mean total hourly maximum dose of .093 mg/hr, is minimal when compared with the recommendation in the report by Trentadue and colleagues (1998). In that retrospective study, one group had low basal rates (.01 to .03 mg/kg/hr), but a higher PCA dose (.25 mg/kg/dose), and a higher total hourly maximum starting dose of approximately 0.1 to 0.15 mg/kg/hr than the PCA regimen in the current study. A second group was prescribed a different regimen with a higher basal rate (0.05 to 0.2 mg/kg/hr), a lower PCA dose (0.01 to 0.02 mg/kg/dose), and the same total hourly maximum of 0.05 mg/ to 0.2 mg/kg/hr than the first group. The first group used significantly less morphine during hospitalization, had a shorter number of days on PCA, had lower costs of PCA pump rental and morphine syringes, and had lower pain scores in both ratings of worst and least pain than the second group. The PCA regimen (low basal rate, low PCA dose, and low total hourly maximum) in the current study is even less optimal than the regimen (high basal rate, low PCA dose) that was previously reported to be a less effective PCA regimen. This may explain why pain intensity did not show a clinically significant decrease during hospitalization.

It is possible that health care providers in the current study were not prescribing a more optimal regimen because they were noting that patients were not using what was already prescribed. Another alternative explanation may be that the effects of opioids on respiratory effort may be particularly problematic in sickle cell disease, especially given that the majority of the patients presented with pain in the chest.

Pain Relief

Children indicated little relief from analgesic medications during nighttime, daytime, and current time with mean relief scores of 3.9, 3.3, 3.6, respectively, on 0 to 10 NRS. The APS Guideline for the Management of Pain in Sickle Cell Disease (Benjamin et al., 1999) defines relief as a score of 5 or greater on a pain relief scale (0=did not help at all to 10=helped a lot). Significant relief has not been achieved if a patient rates 0 to 3 on the (0 to 10 NRS) pain relief scale and titration should continue until the highest achievable relief scores for each individual are achieved, or until side effects become problematic.

The finding that relief was not maximized is consistent with the finding that the pain intensity did not show a clinically significant change. Pain relief was not maximized during hospitalization most likely because the amount of analgesics used was small. The quality of pain described by the children should be responsive to opioids. The fact that pain intensity did not show a clinically significant decrease and pain relief was not maximized during hospitalization suggests that clinicians were not titrating analgesics to maximize relief and the PCA regimen administered was not optimal.

It is not surprising that no significant relationships were found between changes in pain relief scores and amount of analgesic used, and between the amount of analgesic used and changes in either current or worst pain intensity. The reason for the lack of relationship is most likely due to the small amount of analgesics used.

This study is the first to use a pain relief scale to evaluate the effectiveness of pain medications in children with sickle cell disease. Generally, patients' responses to therapy

are evaluated using pain intensity scores. Pain relief scores are another means of evaluating responses to therapy.

Conclusions

Current pain, worst pain, and least pain decreased by 5% during hospitalization, which was not clinically significant. A large inter-individual variability in the amount of change was evident and up to 25% of the episodes showed no change in pain intensity during hospitalization. The inadequate use of self-administered analgesics may be the reason for the lack of significant decreases in pain intensity. Therefore, clinicians need to monitor pain intensity and adjust analgesic doses according to individual needs. Clinicians need to encourage patients to use the amount of medications prescribed, or change the PCA regimen to increase basal rates until patients are able to assume control of pain management.

The number of pain sites marked on the BOD and the surface area decreased significantly during hospitalization. The decrease in the pain location surface area despite low use of analgesics, may be reflective of the fact that inflammation and hemolysis were resolving, and may have been responsive to the effects of ketorolac. Monitoring pain location surface area may be another means of monitoring the effectiveness of pain treatments. Therefore, clinicians may incorporate the use of BOD to monitor changes in the spatial distribution of the pain.

Sickle cell pain was described as having evaluative, sensory, affective, and temporal qualities, which did not change during hospitalization. The lack of change in pain quality may be related to the fact that pain intensity was not decreasing substantially. The constant, aching, and throbbing quality of the reported pain suggests that the pain

experienced by the children in this study is of an ischemic and inflammatory type, which should be responsive to opioids and NSAIDs. Therefore, clinicians may expect a change in pain quality with a corresponding change in pain intensity. The use of word list descriptors may be useful for monitoring pain quality, which is another dimension that has not been evaluated previously.

Both pain intensity and CBC values showed no significant changes during hospitalization. There may be a simultaneous relationship between pain intensity and CBC values. Pain was steady around day 4 to day 6 when hemolysis and inflammation may be resolving, and when the day of discharge may also be occurring. Therefore, CBC values may offer another dimension for monitoring the eventual progression of the vaso-occlusive episode.

Signs and symptoms associated with vaso-occlusion were noted a mean of four days prior to admission, and children were experiencing pain at the same time. By the time they entered the health care system their pain was severe and difficult to control. Therefore, clinicians need to instruct parents to recognize signs and symptoms of impending vaso-occlusive episodes early, and to encourage parents to contact a health care provider for early pain management and prevention of severe pain.

Pain interfered with functional status, such as sleeping, eating, and activity during hospitalization. Functional status is another dimension that needs to be examined when monitoring the effectiveness of treatments. Clinicians may expect an increase in functional status with improvements in the management of pain. Therefore, the use of NRS scales of sleeping, eating, and activity may be useful for monitoring functional status as well as the effectiveness of interventions for pain.

Children were prescribed morphine via PCA, with prescribed PCA doses at high and supra therapeutic levels, and basal rate doses at sub therapeutic and low therapeutic levels. However, despite easy access to an opioid, the children were not self-administering the prescribed amounts. The fears and concerns related to addiction in children with sickle cell disease may be unjustified. Therefore, clinicians need to provide ongoing education to remind patients of the negative consequences related to unrelieved pain and to remind them that the risks of negative outcomes are higher than the risks of psychological addiction.

Children had little relief from medications. The lack of change in MQS scores and in the amount of morphine used during hospitalization suggests that medications may not be titrated to achieve pain relief. Therefore, clinicians need to monitor self-reports of pain relief in relationship to the amount of self-administered analgesics. The use of a NRS may be useful in monitoring pain relief to determine the effectiveness of interventions.

Several limitations in the study need to be mentioned. First, the generalizability of the findings may be limited because the sample size was small, and the 40 episodes represented only 27 patients. Because of the small number of patients, the experiences between the younger and older children could not be differentiated; the results reported may be reflective of the older children. Second, the analysis included second admissions for 7 patients and third admissions for 5 patients. Those patients who had repeat admissions may have had different pain experiences and characteristics than those who had less frequent admissions. Third, the daily repeated measurements may have influenced the participants to respond in the same manner as previous days. Fourth, the

MQS scores represented gross measurement of the amounts of analgesics used over a 24 hour period, and did not address specific interventions during flareups that may have occurred during the day. Fifth, the measures of pain relief and functional status were self-reports, rather than objective measures; these measures were not routinely asked previous to the current study. The children may also have been more honest with the researcher who was not involved in the care. And finally, the statistical procedures used were based on a linear relationship with time, when the relationship may not have been linear.

Recommendations for Future Research

The following recommendations are made for future research:

1. Evaluate whether increasing analgesic use to at least the amount prescribed would lead to a clinically significant decrease in pain intensity, increase the amount of pain relief, and increase in functional status.
2. Evaluate strategies for increasing opioid responsiveness when improvement is not substantial with adequate use of analgesics.
3. Examine whether patients with diffuse pain report a higher level of pain intensity, that are more difficult to control than those patients who had more localized pain.
4. Examine whether patients with more frequent or repeat admissions have a higher level of pain intensity than patients who had less frequent admissions.
5. Evaluate whether pain experience, pain management, and pain outcomes are different between younger and older children.
6. Examine the relationship between pain intensity and CBC values with a larger sample size.

7. Compare results and conclusions with use of other statistical procedures such as individual regression analysis, which would allow examination of individual responses over time, or time series analysis, which would allow for examination of simultaneous relationships of variables over time.

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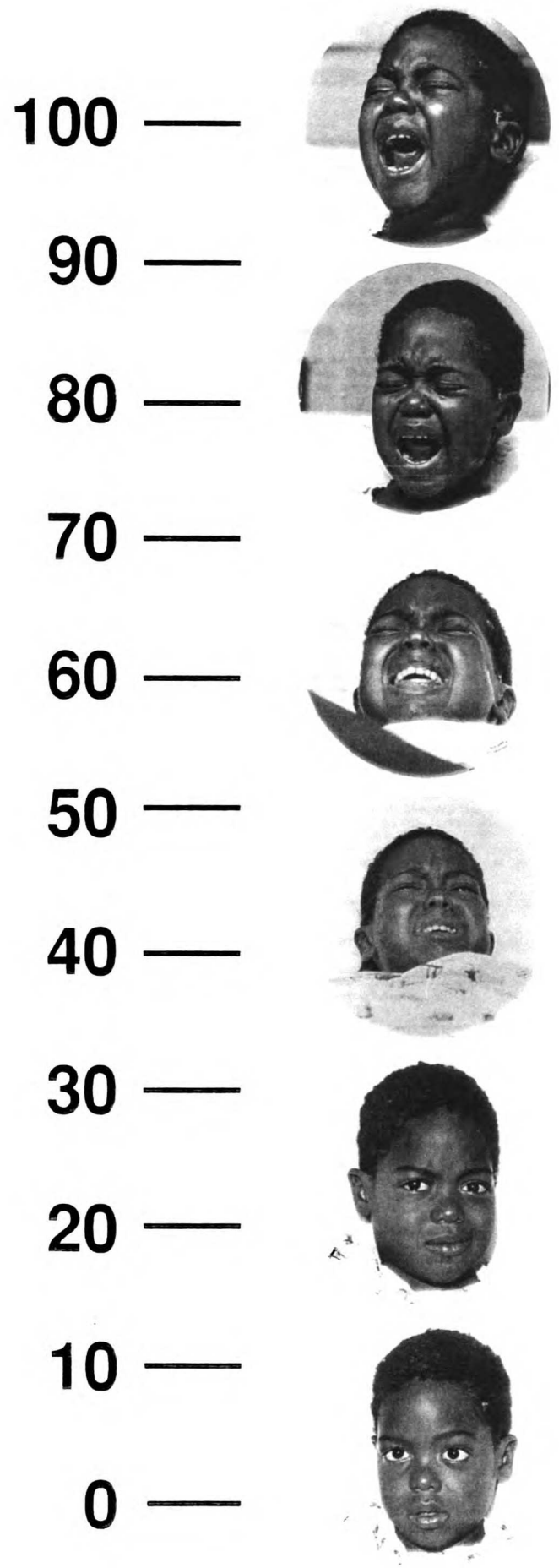
Appendix A
Oucher Pain Scale

OUCHER®



THE OUCHER: A SUMMARY

What is the OUCHER?

The OUCHER is a poster developed for children to help them communicate how much pain or hurt they feel. There are two scales on the OUCHER: A number scale for older children and a picture scale for younger children.

Which scale should be used?

Children who are able to count to 100 by ones or tens and who understand, for example, that 71 is greater than 43, can use the numerical scale. Children who do not understand numbers should use the picture scale. Some children who are able to use the number scale might prefer to use the picture scale. Ask the child which scale he or she would prefer.

How do I use the OUCHER?

Picture scale: The following is an example of how to explain the picture scale to a younger child. The words can be changed when using the picture scale with an older child.

This is a poster called the OUCHER. It helps children tell others how much hurt they have. (For younger children, it might be useful to ask: Do you know what I mean by hurt? If the child is not sure, then an explanation should be provided.) Here's how this works. This picture shows no hurt (point to the bottom picture), this picture shows just a little bit of hurt (point to the 2nd picture), this picture shows a little more hurt (point to the 3rd picture), this picture shows even more hurt (point to the 4th picture), this picture shows a lot of hurt (point to the 5th picture) and this picture shows the biggest hurt you could ever have (point to the 6th picture). Can you point to the picture that shows how much hurt you are having right now?

Once a child selects a picture, their picture selection is changed to a number score from 0 to 5.

5 - Picture at the top of the scale
4 - Second picture from the top
3 - Third picture from the top
2 - Fourth picture from the top
1 - Fifth picture form the top
0 - Picture at the bottom of the scale

Number scale: The following is an example of how to explain the number scale.

This is a poster called the OUCHER. It helps children tell others how much hurt they have. Here's how it works. 0 means no hurt. Here (point to the lower third of the scale, about 10 to 30) this means you have little hurts: here (point to the middle third of the scale, about 30 to 60) it means you have middle hurts. If your hurt is about here (point to the upper third of the scale, about 60 to 90) it means you have big hurts. But, if you point to 100, it means you have the biggest hurt you could ever have. Can you point to the number (or tell me which number) that is like the hurt you are having right now?

The pain score for the number scale is the exact number from 0 to 100 that the child gives you.

What does the score mean? How should it be used?

The person who has pain is the expert or the one who knows best how the pain feels. The OUCHER score gives parents, teachers, nurses, and doctors some idea of how much pain the child is feeling. OUCHER scores can be used as a means to see if certain actions used to relieve pain, such as rest, applying heat or cold, eating or drinking, and medicine make a difference in how much pain the child feels. OUCHER scores can be recorded over a period of hours or days and would be useful information to share with nurses and doctors.

Remember, OUCHER scores only communicate how much pain the child is feeling. Other observations, such as changes in activity, location of the pain, what it feels like, and how long it lasts, are important. If you, as a parent or teacher, are concerned about the child's pain, you should contact your health care provider.

Appendix B
Adolescent Pediatric Pain Tool

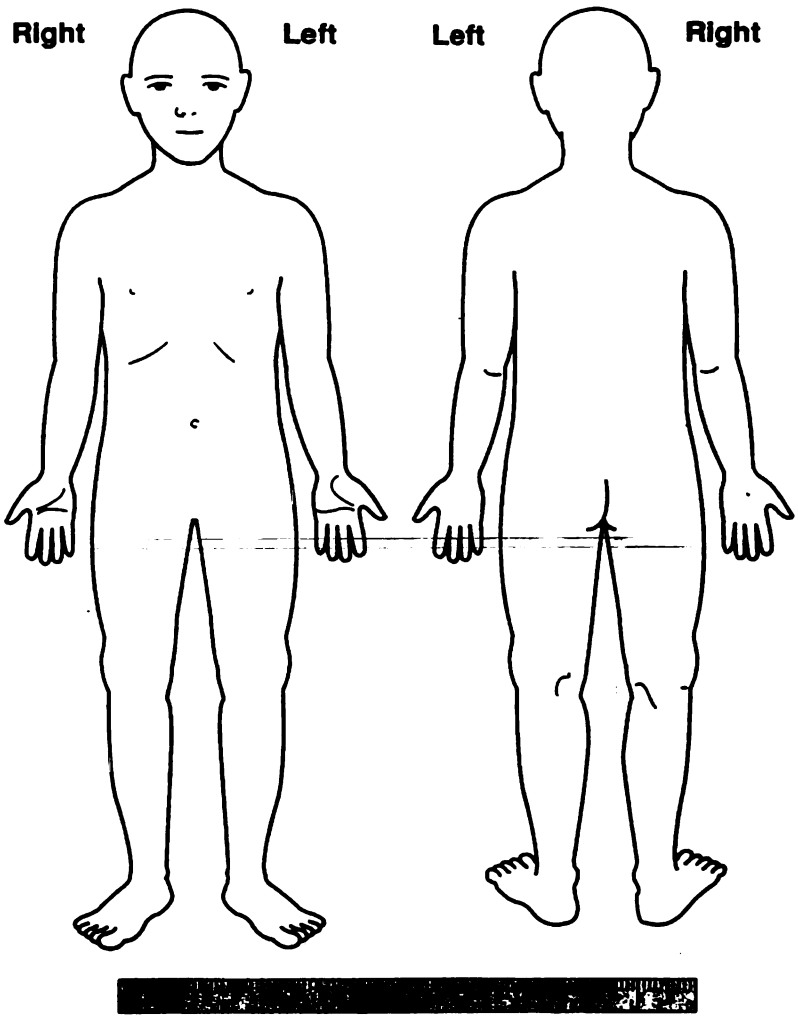
CODE _____

DATE _____

ADOLESCENT PEDIATRIC PAIN TOOL (APPT)

INSTRUCTIONS:

1. **Color in the areas on these drawings to show where you have pain. Make the marks as big or small as the place where the pain is.**



2. Place a straight, up and down mark on this line to show how much pain you have.

3. Point to or circle as many of these words that describe your pain.

1
annoying
bad
horrible
miserable
terrible
uncomfortable

2
aching
hurting
like an ache
like a hurt
sore

3
beating
hitting
pounding
punching
throbbing

4
biting
cutting
like a pin
like a sharp knife
pin like
sharp
stabbing

5
blistering
burning
hot

6
cramping
crushing
like a pinch
pinching
pressure

7
itching
like a scratch
like a sting
scratching
stinging

8
shocking
shooting
splitting

9
numb
stiff
swollen
tight

10
awful
deadly
dying
killing

11
crying
frightening
screaming
terrifying

12
dizzy
sickening
suffocating

13
never goes away
uncontrollable

14
always
comes and goes
comes on all of a sudden
constant
continuous
forever

15
off and on
once in a while
sneaks up
sometimes
steady

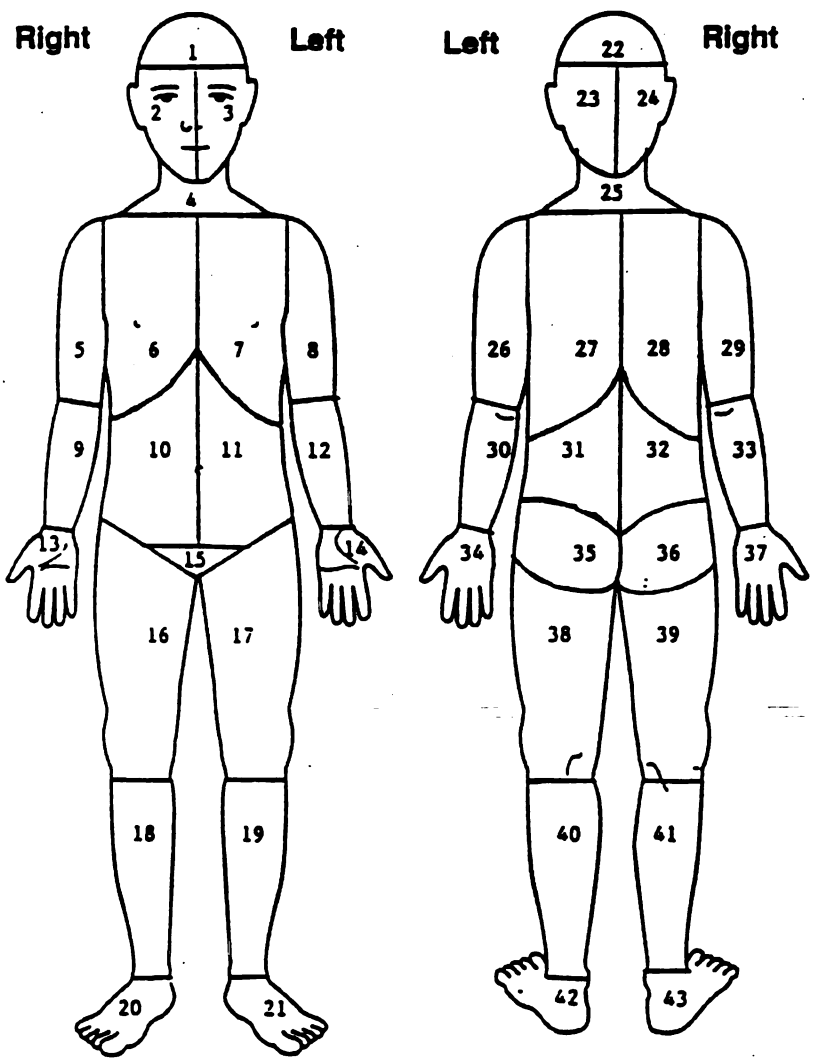
If you like, you may add other words:

_____
_____
_____

For office use only.

BSA: _____		
IS: _____		
#S(2-9)	_____/37=	_____%
#A(10-12)	_____/11=	_____%
#E(1,13)	_____/8=	_____%
#T(14,15)	_____/11=	_____%
Total	_____/67=	_____%

This template is used to make a transparency to overlay onto the Body Outline marked by the child/adolescent in order to score the location of pain.



SCORING THE ADOLESCENT PEDIATRIC PAIN TOOL (APPT)

1. Body Outline

   Using a template*, note the number of body spots where pain is marked and record the number on side 2 of the APPT (BSA:). The location is noted and also recorded, i.e., #1 - 43.

2. Word Graphic Rating Scale

   The ruler on the bottom of side 1 is used to obtain a numerical pain intensity score. It is recorded on side 2 of the APPT (IS:).

3. The number of words selected in each of the four categories:

   a. Sensory Words (S) found in groups 2 - 9 (n = 37)
   b. Affective Words (A) found in groups 10 - 12 (n = 11)
   c. Evaluative Words (E) found in groups 1 and 13 (n = 8)
   d. Temporal Words (T) found in groups 14 - 15 (n = 11).

   The total number of words is recorded. The percentage of words in each category can be obtained by dividing the words circled by the number of possible words in each category.

*Adapted from Margolis, R.B., Tait, R.C., Krause, S.J., (1986). A rating system for the use with patient pain drawings. Pain, 24, 57-65.

**For more information please contact Marilyn Savedra, DNS, RN or Mary Tesler, MS, RN, Dept. of Family Health Care Nursing, University of California, San Francisco, San Francisco, CA, 94143

Appendix C
Numeric Rating Scales for Sleeping, Eating, Activity, and Pain Relief

Measure of Functional Status

Sleeping – How much sleep did you have last night?

0	1	2	3	4	5	6	7	8	9	10
did not sleep at all		slept a little		slept some		slept quite a bit			slept a lot	

Sleeping – How much sleep did you have during the day?

0	1	2	3	4	5	6	7	8	9	10
did not sleep at all		slept a little		slept some		slept quite a bit			slept a lot	

Eating – How much did you eat today?

0	1	2	3	4	5	6	7	8	9	10
didn't eat anything		ate a little bit		ate some		ate quite a bit			ate a lot	

Activity - How much did you do today?

0	1	2	3	4	5	6	7	8	9	10
didn't do anything		did a little bit		did some		did quite a bit			did a lot	

Measure of Pain Relief

Pain relief during the night – How well did the medicines help you with your hurt during the night?

0	1	2	3	4	5	6	7	8	9	10
didn't help at all		helped a little bit			helped some		helped quite a bit			helped a lot

Pain relief during the day – How well did the medicines help you with your hurt during the day?

0	1	2	3	4	5	6	7	8	9	10
didn't help at all		helped a little bit			helped some		helped quite a bit			helped a lot

Pain relief now – How well are the medicines helping you with your hurt right now?

0	1	2	3	4	5	6	7	8	9	10
didn't help at all		helped a little bit			helped some		helped quite a bit			helped a lot

Appendix D
Signs and Symptoms Checklist

Signs & Symptoms Checklist

The child is observed for the following signs and symptoms each day:

Circle those that were observed in the last 24 hours:

General

Fever dizzy weak pallor tired yellowing of the eyes
Other _____

Respiratory
change in the way child breathes difficulty with breathing coughing
change in RR change in O2 sats other _____

Musculoskeletal:
swelling of hands/feet joint tenderness joint stiffness
other _____

Gastrointestinal:
Vomiting little or no appetite diarrhea stomach getting bigger
Other _____

Skin:
change in color rashes itching ulcers
Other _____

Total Number of Signs & Symptoms observed _____

The child's CBC Result is recorded each day.

WBC	
RBC	
Hgb	
Hct	
Plts	
Retics	

Appendix E
Medication Quantification Scale Worksheet & List of Medications

MEDICATION QUANTIFICATION SCALE WORKSHEET

Medications	Total 24 hr Dose Range Recommended** based on kg wt		Total 24 hr Dose Prescribed		MQS Prescribed		Total 24 hr Dose Administered		MQS Administered	
	LO	HI	Amt	DL	DW X DL		Amt	DL	DW X DL	
Acetaminophen					1				1	
Acetaminophen MQS TOTAL Scores										
Ibuprofen					2				2	
Ketorolac					2				2	
NSAIDs MQS TOTAL Scores										
Amitriptyline					2				2	
Antidepressants MQS TOTAL Scores										
Diphenhydramine					3				3	
Flexeril					3				3	
Relaxants MQS TOTAL Scores										
Vicodin					4				4	
Percocet					4				4	
Acetaminohen with codeine					4				4	
Lorazepam					4					
Converted to MS					6				6	
Converted to MS					6				6	
Converted to MS					6				6	
Weak Opioids MQS TOTAL Scores										

Morphine					6				6	
MS Bolus										
Morphine PCA										
Morphine BR										
MS Lockout										
MS Max					6				6	
Dilaudid					6					
Strong Opioids MQS TOTAL Scores										
TOTAL MQS SCORES										

*Taketomo, C. K., Hodding, J. H., & Kraus, D. M. (1999). *Pediatric Dosage Handbook*. Hudson, Ohio: Lexi-comp, Inc.

**DW: Detriment Weight: 8 classes of medications frequently prescribed for pain and a detriment weight assigned, based on potential detrimental effects with long-term use (from 1=low potential for adverse effects to 6=high potential for undesirable effects)

***DL: 1 = Subtherapeutic 2=Low Therapeutic 3=Hi Therapeutic 4=Supratherapeutic

(Adapted from: Steedman, S. M., Middaugh, S. J., Carson, W. G. K. S., Harden, N., & Miller, M. C. (1992). Chronic-pain medications: Equivalence levels and method of quantifying usage. The Clinical Journal of Pain, 8(3), 204-213.

Medication Quantification Scale Scoring Guide

Medication Class	Detriment Weight
Acetaminophen/aspirins	1
NSAIDS	2
Antidepressants	2
Skeletal muscle relaxants	3
Benzodiazepines/antianxiolytics	4
Weak Narcotic Analgesics	4
Barbiturates/sedatives	5
Strong Narcotic Analgesics	6

Administered Amount	Dosage Level
Subtherapeutic dose (less than recommended dose)	1
Low therapeutic dose (lower half of daily dosage range)	2
High therapeutic dose (upper half of daily dosage range)	3
Supratherapeutic dose (greater than recommended)	4

Medications Most Commonly Used in Children With Sickle Cell Disease

Acetaminophen	10-15 mg/kg/dose q 4 650 mg q 4-6 (>50kg)

NSAIDS

Ibuprofen	4-10 mg/kg/dose q 6-8 400-800mg q6 (>50kg)
Ketorolac	.5 – 1mg/kg/dose q 6 not to exceed 30 mg/dose 15-30mg q6; not to exceed >5 days or 120mg/day (>50kg)
Viox	25 mg; 1-2x/day

ANTIDEPRESSANTS

Amitriptyline	.5 to 2 mg/kg q HS

ANTIANXIETY/RELAXANTS

Ativan	.05mg/kg/dose; max 2 mg/dose; q 4-8 hours; range .02-.1 mg/kg/dose
Diphenhydramine	1mg/kg/dose or 5mg/kg/day >50 kg: 10-50/dose q 4 hours; up to 400 mg/day maximum
Flexeril	20-40mg/day in 2-4÷doses
Tramadol	DW: 4 Dose: 50-100 mg every 6-8 hrs

WEAK OPIOIDS

Vicodin	.6mg/kg/day; not to exceed 1.25 mg/dose < 2 yo 5mg/dose for 2-12 yo; or 10mg/dose for >12 yo
Vicoprofen	1-2 tabs q 4-6; max 5 tabs per day
Percocet	.05-.15 mg/kg/dose (oxycodone); max 5mg q4-6; 1-2 tabs q4-6
Tylenol + codeine	.5 – 1mg/kg/dose q 6 (cod) 15-60 q4-6 hrs; usual 30 mg/dose

EQUIVALENTS

Tylenol in Tylenol #3	300mg/tab Tylenol, 30 mg/tab codeine
Tylenol in Tylenol #4	300mg/tab Tylenol, 60 mg/tab codeine
Tylenol elixir	120mg/5 ml Tylenol, 12mg/5 ml codeine

Tylenol in Percocet	500 mg/tab, 5 mg/tab oxycodone
Tylenol in Vicodin	500mg/tab Tylenol, 5 mg/tab hydrocodone (.6 mg/kg/day); in adults 1-2 tabs q4to 6 hrs prn
Ibuprofen in Vicoprofen	200 mg ibuprofen/7.5 mg hydrocodone

IV CONVERSIONS

1 mg IV MS = 20 mg PO codeine
1 mg IV MS = 3 mg PO MS = 3 mg Hydrocodone = 3 mg Oxycodone
1 mg IV MS = 10 mg IV Demerol
10 mg IV MS = 1.5 dilaudid
6.66 mg IV MS = 1 mg dilaudid

STRONG OPIOIDS

Morphine	.1 - .2 mg/kg/dose IV q 2-4 hrs, usual max 15mg/dose >50 kg: 2.5-20 mg/dose IV q 2-6hrs; usual 10mg/dose q 4 prn .2 to .5 mg/kg/dose PO q 4-6 hours, for <50 kg; .3 to .6 mg/kg/dose PO q 12 (controlled release) 50 kg: 10-30 mg PO q 4 prn; controlled release 15-30mg PO q 8-12hrs
MS Bolus	.03 to .1mg/kg
Morphine PCA	.01 - .03 mg/kg
Morphine BR	.01 mg/kg/hr initially; continuous infusion: .025-2.6mg/kg/hr
MS Lockout	10 to 30 minutes
MS q hr Max	.1mg/kg/hr to 6-8 mg/hr, initially For >50 kg .8-10 mg/hr, usual range up to 80 mg/hr increase as needed to an amount that would relieve the pain
Meperidine	1-1.5 mg/kg/dose q 3-4 hrs; max 100 mg/dose Adults 50-100 mg/dose q 3-4 hrs
Meperidine Bolus	.5 to 1 mg/kg
Meperidine PCA	.3 mg/kg
Meperidine BR	.3 mg/kg/hr initially; continuous infusion: .5-.7mg/kg/hr
Meperidine Lockout	10 to 30 minutes
Meperidine q hr Max	.1mg/kg/hr to 6-8 mg/hr, initially For >50 kg .8-10 mg/hr, usual range up to 80 mg/hr increase as needed to an amount that would relieve the pain
Dilaudid	PO: .03-.08 mg/kg/dose q 4-6 hrs prn, max 5 mg/dose IV: .015 mg/kg/dose q4-6 hrs prn as needed Older children & adults: PO, IV, IM, SQ: 1-4mg/dose q4-6 hrs prn Usual adult dose 2mg/dose

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Taketomo, C. K., Hodding, J. H., & Kraus, D. M. (1999). *Pediatric Dosage Handbook.* Hudson, Ohio: Lexi-comp, Inc.; Benjamin, L.J., Dampier, C.D., Jacox, A.K., Odesina, V., Phoenix, D., Shapiro, B., Strafford, M., & Treadwell, M. (1999). Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease, APS Clinical Practice Guidelines Series, No. 1. Gleview, IL: American Pain Society.

Appendix F
Letters of Approval

Committee on Human Research, University of California San Francisco
Medical Research Committee, Children's Hospital Oakland
Institutional Review Board, Children's Hospital Oakland
Executive Board, Children's Hospital Oakland

COMMITTEE ON HUMAN RESEARCH
OFFICE OF RESEARCH ADMINISTRATION, Box 0962
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
www.ucsf.edu/ora/chr

CHR APPROVAL LETTER

TO: Christine Miaskowski, Ph.D., R.N.
Box 0610

cc Eufemia Jacob, M.S.N.
25865 Meadowmist Drive
Hayward, CA 94544

RE: Pain in Children with Sickle Cell Disease

The Committee on Human Research (CHR), the UCSF Institutional Review Board (IRB) holding Department of Health and Human Services Multiple Project Assurance #M-1169, has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter.

APPROVAL NUMBER: H7025-17123-01 .This number is a UCSF CHR number and should be used on all correspondence, consent forms and patient charts as appropriate.

APPROVAL DATE: March 1, 2000. **Full Committee Review**

EXPIRATION DATE: March 1, 2001. If the project is to continue, it must be renewed *by the expiration date*. See reverse side for details.

ADVERSE EVENT REPORTING: All problems having to do with subject safety must be reported to the CHR within ten working days. All deaths, whether or not they are directly related to study procedures, must be reported. Please review Appendix A of the CHR *Guidelines* for additional examples of adverse events or incidents which must be reported.

MODIFICATIONS: Prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol which affect subjects.

QUESTIONS: Please contact the office of the Committee on Human Research at (415) 476-1814 or campus mail stop, Box 0962, or by electronic mail at chr@itsa.ucsf.edu.

Sincerely,

Arthur Ablin

Arthur R. Ablin, M.D.
Chairman
Committee on Human Research

Children's Hospital Oakland

March 24, 2000

Eufemia Jacob, RN, PhD(c)
25865 Meadowmist Drive
Hayward, CA 94544

Dear Eufemia:

Your proposal entitled, "Pain in Children with Sickle Cell Disease" was approved by the Children's Hospital Oakland Research Committee at the March 24, 2000 meeting. Your proposal has been automatically forwarded to both the Executive Committee and the Institutional Review Board (IRB).

The Executive Committee will briefly review your study and return any comments or questions to the Research Committee. You are not expected to attend the Executive Committee meeting, or to prepare any additional paperwork.

The IRB will be reviewing your study at their April 20, 2000 meeting. You (and your staff sponsor if appropriate) are expected to be at this meeting to discuss your proposal.

Following approval by the Executive Committee, and final approval by the IRB, you will be notified by letter. Until you have received these letters, you may not begin your study.

If you should have any further questions about this process, please call Jean Doty in the Research Department at (510) 428-3173.

Sincerely,

David Durand

David Durand, M.D.
Chairman, Research Committee

DD/jd

ps — Good luck with your study

The pediatric medical center for Northern California

747 Fifty Second Street
Oakland, CA 94609-1809
510-428-3000

Children's Hospital Oakland

May 18, 2000

Eufemia Jacob, RN, PhD(c)
25865 Meadowmist Drive
Hayward, CA 94544

Dear Dr. Jacob:

Thank you for sending us the revised consent for your study entitled, "Pain in Children with Sickle Cell Anemia". As chairman of the Institutional Review Board (IRB), I find that the changes in the consent form comply with the suggestions made at the IRB meeting. This form should satisfy ethical considerations. A copy of the signed consent form must be kept with each patient's medical records.

Please notify us if you do not get funding for this study. We will then assume it is closed.

As of this date, your project is approved by the IRB. When you receive Executive Committee approval, you may begin your study. In approximately nine months, you will receive a letter advising when the IRB will again review your study.

If you wish to make any changes in your project or the consent form, you must seek prior approval from the IRB.

Sincerely,

Rose Ellen Morrell, M.D.
Chairman
Institutional Review Board

REM:jd

The pediatric medical center for Northern California

747 Fifty Second Street
Oakland, CA 94609-1809
510-428-3000

Children's Hospital Oakland

May 18, 2000

Eufemia Jacob, RN, PhD(c)
25865 Meadowmist Drive
Hayward, CA 94544

Dear Dr. Jacob:

Pursuant to the March 24, 2000 recommendation of the Research Committee, the Children's Hospital Oakland Executive Committee approved your study entitled, "Pain in Children with Sickle Cell Anemia" on April 11, 2000.

You now have final approval and may begin your study.

Should you have any questions, please feel free to contact me at (510) 428-3173.

Sincerely,

Jean Doty,
Research Secretary

The pediatric medical center for Northern California

747 Fifty Second Street
Oakland, CA 94609-1809
510-428-3000

Appendix G
Demographics and Medical Information Form
And Child Parent Interview Form

Demographic and Medical Information Form

Demographics

weight in kg: _____
date of birth: _____
hemoglobin phenotype: SS SC Sβ _____
gender: M F
date _____ and reason for hospitalization (if child is hospitalized):
fever pneumonia pain acute chest
splenic sequestration infection
other _____

Date when first signs/symptoms noted by family: _____
Date when child first felt pain: _____
Date when family first contacted health care provider: _____
Point of first contact: MD Office/Clinic ER Day Hospital
Date when child was admitted: _____
Total number of days for this hospitalization: _____
Date since last visits
ER: _____
Sickle Cell Clinic: _____
Day Hospital: _____
Acute Care Unit: _____

Review the medical records and obtain the following information:

Check if the child has or had previous history of the following since diagnosis of sickle cell disease:

_____stroke
_____acute chest syndrome
_____ avascular necrosis
_____infections
_____duodenal ulcers
_____cholecystitis
_____splenic sequestration
_____rib infarcts
_____leg ulcers
_____pneumonia
_____pancreatitis
_____psychotic disorders
_____any other illnesses and conditions_____
_____
_____

_____number of times for clinic visits in the past 12 months
reasons for clinic visits _____

_____number of times for ER visits in the past 12 months
reasons for ER visits_____

_____number of times for hospitalizations in the past 12 months
reasons for hospitalizations_____

Multidisciplinary Interventions.

Child is meeting with the following professionals on a regular basis:

_____Physical Therapist
_____Psychologist
_____Child Life Volunteer
_____Play Therapist
_____Social Worker
_____Home/Hospital Teacher
_____Other _____

Disease Related Interventions.

_____ chronic PRBC transfusion therapy
_____hydroxyurea
_____bone marrow transplant
_____exchange transfusion
_____desferal
_____other_____

Comments:

Child/Parent Interview Form

At the time of enrolment the parent/primary caregiver will be asked about the onset of child's pain.

1. When did the pain start?

2. Was there any signs and symptoms you noted before child complained of pain? if yes, circle them in the Signs & Symptoms Checklist.

3. On the Oucher Pain Scale how would you rate the child's pain when it started?

   NRS _____ Faces _____

4. Did it start gradually, intermittently, suddenly?

6. Was it constant or off and on?

7. How would you rate your child's pain now using the Oucher Pain Scale?
   NRS _____ Faces _____

8. What medications, how much, and how often did you give them?

9. How much did the medications helped?

0	1	2	3	4	5	6	7	8	9	10
didn't help at all		**helped a little bit**			**helped some**		**helped quite a bit**			**helped a lot**

10. Is there anything else you want to tell about the onset of this episode?

11. How does this episode compared to the other episodes your child had?

12. Comments

Data Collection Tool

A. Pain Intensity Using the Oucher Pain Scale

Present Pain

Point to the picture that shows how much hurt you are having right now? _____
If child is 8 to 19 years also ask:
Point to the number that is like the hurt you are having right now? _____

Worst Pain

Was there ever a time during the night or day when you had more pain than what you are having right now? No ___ Yes ____
Point to the picture that shows how much was the worst hurt you had? _____
(If child is 8 to 19 years):
Point to the number that is like the worst hurt you had? _____

Least Pain

Was there ever a time during the night or day when you had less pain than what you are having right now? No ___ Yes ____
Point to the picture that shows how much was the smallest hurt you had? _____
(If child is 8 to 19 years):
Point to the number that is like the smallest hurt you had? _____

B. Pain Location using Body Outline Diagram of the APPT

When you had the most hurt, color in the areas on these drawings to show where it hurts when you were having the most hurt.
Make the marks as big or small as the place where the hurt is.

C. Pain Quality using the Word Descriptor List of the APPT

Point or circle as many of these words that describe the hurt when you were having the most hurt you felt today.
(For the child who is unable to read, read one word group at a time and ask the child).

Recruitment and Enrollment Log

The researcher completes this form and enters the information for each child enrolled in the study.

Name of Child	Date of Birth	MMR #	Name of Parent	Telephone # Beeper #	Child Assent Signed	Consent Signed

Appendix J
Child Assent and Parent Consent Form

Children's Hospital Oakland

CHO/IRB
MAY 1 8 2000
Approved

CONSENT TO BE A RESEARCH PARTICIPANT
Pain in Children With Sickle Cell Disease

PURPOSE OF THE STUDY

The purpose of this research study is to describe the pain experience of children with sickle cell disease in the hospital. Because you have sickle cell disease, you are being asked to be part of the study.

SPONSORSHIP

This study is being conducted by the Department of Nursing, Hematology/Oncology Unit, at Children's Hospital Oakland. Eufemia Jacob, RN, a nurse in the Hematology/Oncology Unit is primarily responsible for conducting this study. Eufemia Jacob may be reached at (510) 428-3339.

PROCEDURES

Because you are having pain, you are being asked to participate in the following study. If you are willing to be part of this study, Eufemia Jacob will ask you some questions about your pain, from the time it started until you came to the hospital.

Eufemia will ask you to describe how much pain you are having. She will also ask you to color in a body outline where the pain is and what words from the list describes the pain you are feeling. She will record all the medicines you received for pain. She will ask how much the medicines helped during the day and night. She will also ask how much sleeping, eating, and activity you had during the day. This takes no more than ten minutes to do.

In addition, Eufemia will observe you for specific signs and symptoms of illness, using a checklist. She will also get information from your medical records such as results of CBC, past medical history, medications and treatments you received.

SAFETY/RISKS/DISCOMFORTS

You may find it tiring to answer the questions. You may refuse at any time. If you do not want to answer the questions, the session will be ended.

BENEFITS

There are no direct benefits to you by being in the study. However, the information gained from this study may help to make changes in the way that pain is assessed and managed in children with sickle cell disease.

The pediatric medical center for Northern California

747 Fifty Second Street
Oakland, CA 94609-1809
510-428-3000

ALTERNATIVES

Whether you choose to take part in this study or not, you will continue to receive up-to-date care. You may choose not to participate in this study.

CONFIDENTIALITY

Information collected from you and about you will be handled as confidentially as other medical records. All information for this study will be kept in locked files. Only those who are directly involved in the study will have access to the files. All reports will not identify you by name.

FINANCIAL

To thank you for your participation in this study, you will be able to choose a $20 gift certificate from either McDonald's, Toys R Us, or Musicland/Sam Goody. You will receive this on the day you go home.

INJURIES

There is no injury associated with being in this study. In the rare event that you have discomfort as a result of being in this study, Dr. Lori Styles will be notified immediately. You will be treated at Children's Hospital Oakland at no charge to you or your insurance company. If you wish further information about this, please speak with Eufemia Jacob, RN at (510) 428-3339.

QUESTIONS

If you have any questions, either before being in this study or during the study, please ask Eufemia Jacob who may be reached at (510) 428-3339. Also, if you wish to speak to a doctor who is not involved with this study, you may contact:

Director, Medical Research
Children's Hospital Oakland
747-52nd Street, Oakland, CA 94609
(510) 428-3331

PARTICIPATION IN RESEARCH IS VOLUNTARY

You have the right to refuse to take part in this study. You may withdraw at any time and your medical care will continue at Children's Hospital.

CONSENT TO BE A RESEARCH PARTICIPANT AND LIST OF RIGHTS

Your signature below indicates that you consent to being in this study. You will be given a copy of this form and a copy of the "List of Rights of a Participant in a Medical Experiment" to keep.

AGREEMENT OF CHILD TO PARTICIPATE

If this project has been explained to you and you have had the chance to ask all the questions you want and you agree to take part, please sign below.

_____	_____
Date	Signature of child
_____	_____
Date	Witness

STATEMENT OF INVESTIGATOR

The undersigned hereby certifies that he or she has discussed the research project "Pain in Children with Sickle Cell Disease" with the parents of the participant and the participant, and has explained all of the information contained in the consent form including any adverse reactions that may reasonably be expected to occur. The undersigned further certifies that all those participating in the discussion were encouraged to ask questions and that all questions were answered.

_____	_____
Date	Signature of investigator

CONSENT TO BE A RESEARCH PARTICIPANT
Pain in Children With Sickle Cell Disease

PURPOSE OF THE STUDY

The purpose of this research study is to describe the child's pain experience in the hospital during the painful episodes. Because your child has sickle cell disease, he or she is being asked to be part of the study.

SPONSORSHIP

This study is being conducted by the Department of Nursing, Hematology/Oncology Unit, at Children's Hospital Oakland. Eufemia Jacob, RN, a nurse in the Hematology/Oncology Unit is primarily responsible for conducting this study. Eufemia Jacob may be reached at (510) 428-3339.

PROCEDURES

Because your child is hospitalized with a painful episode at Children's Hospital Oakland, you are being asked to participate in the following study.

If you and your child are willing to be part of this study, Eufemia Jacob will ask you some questions about the onset of your child's painful episode, from the time it started until your child was admitted to the hospital.

Eufemia Jacob will ask your child to describe how much pain your child is having. She will also ask your child to color in a body outline where the pain is and what words from the list describes the pain your child is feeling. She will record all the medicines your child received. She will ask how much the medicines helped during the day and night. She will also ask how much sleeping, eating, and activity your child had during the day. This takes no more than ten minutes to do.

In addition, Eufemia will observe your child for specific signs and symptoms of illness, using a checklist. She will also obtain information from your child's medical records such as results of CBC, past medical history, medications and treatments your child received.

SAFETY/RISKS/DISCOMFORTS

Your child may find it tiring or tedious to answer the questions. Your child has the right to withdraw at any time. If your child does not want to answer the questions, the session will be ended.

The pediatric medical center for Northern California

747 Fifty Second Street
Oakland, CA 94609-1809
510-428-3000

BENEFITS

There are no direct benefits to your child by being in the study. However the information gained from this study may help to make changes in the way that pain is assessed and managed in children with sickle cell disease.

ALTERNATIVES

Whether you choose to have your child take part in this study or not, your child will continue to receive up-to-date care. Alternatives for you and your child include refusal to participate in this study.

CONFIDENTIALITY

The child's research data will be handled as confidentially as other medical records. All data for this study will be kept in locked files and only those who are directly involved in the study will have access to the files. Only group data will be reported and any published data will not identify participants by name.

FINANCIAL

To thank you for your participation in this study, your child will be able to choose a $20 gift certificate from either McDonald's, Toys R Us (for the younger child), or Musicland/Sam Goody (for the older child). Your child will receive this on the day he or she goes home.

INJURIES

There is no injury associated with being in this study. In the rare event that your child has discomfort as a result of being in this study, Dr. Lori Styles will be notified immediately, and your child will be treated at Children's Hospital Oakland at no charge to you or your insurance company. If you wish further information about this, please speak with Eufemia Jacob, RN at (510) 428-3339.

QUESTIONS

If you or your child have any questions, either before deciding whether to be in this study or during the course of this study, please discuss your questions to Eufemia Jacob who may be reached at (510) 428-3339. Additionally, if you wish to speak to a physician who is not involved with this research project, and is available for reference, you may contact:

Director, Medical Research
Children's Hospital Oakland
747-52nd Street, Oakland, CA 94609
(510) 428-3331

PARTICIPATION IN RESEARCH IS VOLUNTARY

You have the right to refuse to have your child take part in this study. You may withdraw your child at any time without jeopardizing your child's medical care at Children's Hospital.

CONSENT TO BE A RESEARCH PARTICIPANT AND LIST OF RIGHTS

Your signature below indicates that you consent to your child being in this study. You will be given a copy of this form and a copy of the "Lists of Rights of a Participant in a Medical Experiment" to keep.

Date	Parent's or Guardian's Signature
Date	Parent's or Guardian's Signature
Date	Witness

AGREEMENT OF CHILD TO PARTICIPATE

If this project has been explained to you and you have had the chance to ask all the questions you want and you agree to take part, please sign below.

Date	Signature of child

STATEMENT OF INVESTIGATOR

The undersigned hereby certifies that he or she has discussed the research project "Pain in Children with Sickle Cell Disease" with the parents of the participant and the participant, and has explained all of the information contained in the consent form including any adverse reactions that may reasonably be expected to occur. The undersigned further certifies that all those participating in the discussion were encouraged to ask questions and that all questions were answered.

Date	Signature of investigator