Title

Analgesic efficacy and safety of single-dose intramuscular ketorolac for postoperative pain management in children following tonsillectomy

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Publication Date

1993

Peer reviewed|Thesis/dissertation

ANALGESIC EFFICACY AND SAFETY OF SINGLE-DOSE INTRAMUSCULAR KETOROLAC FOR POSTOPERATIVE PAIN MANAGEMENT IN CHILDREN FOLLOWING TONSILLECTOMY

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco

ACKNOWLEDGEMENTS

This research was supported, in part, by the American Nurse's Foundation; Sigma Theta Tau, Alpha Eta and Alpha Gamma Chapters; University of California, San Francisco, Graduate Division Student Research Award; School of Nursing, Century Club Funds; and Novametrixs Medical System and Critikon Corporations.

I would like to extend my sincere thanks and appreciation to the members of my dissertation committee, including Jon D. Levine, M.D., Ph.D., Suzanne L. Dibble, R.N., D.N.Sc., Marilyn Savedra, R.N., D.N.S., F.A.A.N., and to my chairperson Christine Miaskowski, R.N., Ph.D., F.A.A.N., for their continued support and expertise that contributed to the development and completion of this research. It has been a privilege and an honor to have worked with such a distinguished faculty. I am especially indebted to Christine Miaskowski, my chairperson, advisor, mentor, and friend, who has been a never ending source of motivation, inspiration, and encouragement. Words cannot express my gratitude for your all that you have given of yourself to assure my continued progress, success, and the realization of my highest aspirations.

Finally, a special thanks to my family, especially to my husband Paul, who knew before I did that this day would be a reality. Thank you for your understanding, patience, love, and support throughout these past years. This represents the culmination of both of our efforts, time, and sacrifices to achieve this goal, and the beginning of a lifetime of new and exciting endeavors.

ANALGESIC EFFICACY AND SAFETY OF SINGLE-DOSE INTRAMUSCULAR KETOROLAC FOR POSTOPERATIVE PAIN MANAGEMENT IN CHILDREN FOLLOWING TONSILLECTOMY

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The purpose of this study, in children following tonsillectomy with or without adenoidectomy, was to compare the analgesic requirements, postoperative pain intensity scores, the severity and duration of bleeding, and length of stay between children who received a single intramuscular (IM) dose of normal saline at the completion of surgery (saline group) and children who received a single IM dose of ketorolac at the completion of surgery (ketorolac group).

Children were randomized to receive either an intramuscular (IM) injection of ketorolac (1 mg/kg; ketorolac group, N=45) or saline (1 cc; saline group, N=42) at the completion of the surgical procedure. Intravenous fentanyl (0.5 μg/kg/dose) was administered in repeated doses as needed postoperatively. Pain intensity was measured using the Oucher and the CHEOPS. Severity of postoperative bleeding was measured using a 4-point rating scale. Analgesic measures were obtained prior to each administration of fentanyl and 5 minutes after the drug was given in the Post-Anesthesia Care Unit (PACU), and then hourly until discharge.

The ketorolac group received significantly less fentanyl (mean = 35.9 μg) than the saline group (mean = 48.3 μg, $t=-2.21$, $p<0.03$). In the first hour postoperatively, the CHEOPS demonstrated significant decreases in pain

intensity scores in response to opioids, in both groups. However, during the remainder of the postoperative stay, the photographic scale of the Oucher was the more sensitive and discriminating pain intensity measure. The length of stay of children in the ketorolac group was significantly reduced by approximately 30 minutes. There was no evidence of increased bleeding postoperatively for children in the ketorolac group.

Christine Miaskowski, RN, PhD, FAAN - Chair

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CHAPTER 1

INTRODUCTION

Currently, approximately 50% of all pediatric surgical procedures are performed on an outpatient basis (Bogetz, 1989). With the present emphasis on curtailing health care costs, ambulatory surgery centers are likely to expand their services. Tonsillectomy, with or without adenoidectomy, is one of the most common otolaryngolic surgical procedures performed in children (Richmond, Wetmore & Baranak, 1987; Tami, Parker & Taylor, 1987; Paradise, 1990) and is almost exclusively performed in ambulatory surgery. Current estimates suggest that about 30% of all children in the United States have their tonsils and adenoids removed (Schmitt & Berman, 1987).

The severity of postoperative pain following tonsillectomy, with or without adenoidectomy, is poorly documented. Many times, additional surgical procedures are performed including bilateral myringotomies with tube placement, sinus irrigations, and others, which may contribute to the child's postoperative pain. Children's needs for analgesics following tonsillectomy, with or without adenoidectomy, have ranged from the need for mild analgesics (Kornblut & Kornblut, 1991; Zalzal & Cotton, 1993), to the need for strong opioid analgesics in the immediate postoperative period (Bone & Fell, 1988; Hannington-Kiff, 1985; Steward, 1990). However, few clinical trials have been done to evaluate the efficacy of pharmacologic interventions in the management of postoperative pain in children following adenotonsillectomy. It must be

acknowledged that providing adequate analgesia to this patient population is critically important because unrelieved pain can lead to poor oral intake and subsequent complications associated with hypovolemia.

SIGNIFICANCE

Several issues related to pain management in children underscore the significance of this study. These issues include the undertreatment of postoperative pain in children; the potential for enhanced analgesic efficacy using combinations of analgesics; and the prevalence, severity, and clinical significance of treatment-related side-effects. Each of these issues will be addressed in this section.

The Undertreatment of Postoperative Pain in Children

The undertreatment of postoperative pain in children remains a critical problem. Despite the availability and utility of opioid analgesics to relieve postoperative pain in children, the literature clearly identifies major inadequacies in pediatric pain management. Studies have demonstrated marked reductions in the frequency of analgesic administration (particularly opioid analgesics) in pediatric patients, compared to adults, following similar surgical procedures (Beyer, DeGood, Ashley, & Russell, 1983; Eland & Anderson, 1977; Schechter, Allen, & Hanson, 1986). Others argue that despite the appropriate frequency of administration of opioid analgesics, pain control in children is unsatisfactory due to sub-therapeutic dosing and variable patterns of drug administration (Mather & Mackie, 1983; Bush, Holmbeck & Cockrell, 1989). The plausible consequence

of such actions is increased patient suffering.

The reasons cited for undertreatment include: the prevailing myths that children need little or no pain medicine following surgical procedures; the difficulties associated with accurate pain assessment in children; underprescription of narcotics for children; discrepancies between analgesic prescription and administration; and "as needed" (i.e., p.r.n.) prescription practices which are often associated with decreased drug administration (Beyer et al., 1983; Eland & Anderson, 1977; Schechter, 1989). Although previous studies have examined the care of children in inpatient facilities, practices in ambulatory surgery centers are likely to be influenced by similar obstacles.

The Potential for Enhanced Analgesia Using Combinations of Analgesics

Selection of an analgesic approach, particularly in an ambulatory surgery setting, must promote safety, minimize complications, reduce pain, and facilitate recovery and discharge. Although opioid analgesics have been used as the mainstay in the treatment of postoperative pain in children, recent evidence confirming the powerful effects of inflammatory mediators in primary and secondary hyperalgesia at a peripheral level (Cohen & Perl, 1990; Taiwo & Levine, 1989), suggests a potential role for peripherally acting non-opioid analgesics (i.e., non-steroidal anti-inflammatory drugs [NSAID's]) in enhancing postoperative analgesia. The combined use of a NSAID with an opioid analgesic has been demonstrated to provide improved pain relief in adults with acute or chronic pain (Beaver, 1981). This enhanced or additive analgesic

effect may be due, in part, to the drugs different mechanisms of action. Non-steroidal anti-inflammatory drugs, such as ketorolac, exert their analgesic effects primarily through peripheral mechanisms, specifically through the inhibition of prostaglandin synthesis (Amadio, 1984; Buckley & Brogden, 1990; Kantor, 1984; Mortensen & Rennebohm, 1989; Rooks, Tomolonis, Maloney, Wallach, & Schuler, 1982; Rooks, Maloney, Shott, Wallach, & Schuler, 1985). Whereas, the effects of opioid analgesics are primarily mediated through the central nervous system.

The vast array of pharmacological options for the management of postoperative pain in children provides an opportunity to administer different combinations of analgesics. However, the efficacy of combinations of peripherally and centrally acting analgesics in the treatment of acute postoperative pain in children has not been investigated.

Prevalence and Severity of Side-Effects Using Combinations of Analgesics

In addition to the potential benefit of enhanced pain relief, the use of combined analgesics may alter the incidence and/or severity of particular side-effects. NSAID's have gained widespread use in adults, in part, because of the low incidence of central nervous system side-effects, which are commonly associated with opioid analgesics. Theoretically, the use of a NSAID (e.g., ketorolac) may reduce the total dose of opioid required to achieve analgesia, and subsequently reduce the incidence of opioid-induced side-effects. Clearly,

identification of pharmacologic interventions which provide fewer adverse effects with greater analgesic efficacy is an important research priority.

STATEMENT OF THE PROBLEM

The provision of adequate analgesia is necessary to facilitate smooth emergence from anesthesia and decrease the morbidity during recovery following tonsillectomy, with or without adenoidectomy. Short-acting opioids, such as fentanyl, appear to be useful in outpatient surgery because of their rapid onset and brief duration of action. The pharmacology of fentanyl allows for rapid dose titration and less prolonged sedation. However, most of the experience with fentanyl in children has been during induction and maintenance of anesthesia (Clotz & Nahata, 1991; Koren & Maurice, 1989; Yaster & Desphande, 1988). Data on the efficacy of fentanyl as an analgesic, in children, are extremely limited (Billmire, Neale, & Gregory, 1985; Chen, Wong, Shyr, Chan, & Tan, 1991; Koren & Maurice, 1989; Sandler, Weyman, Conner, Reilly, Dickson, Luzins, & McGorray, 1992; Tobias, 1991; Yaster, Nichols, Deshpande, & Wetzel, 1990).

Recently, the therapeutic effects of non-opioid analgesics in the treatment of postoperative pain have also been identified. Non-steroidal anti-inflammatory drugs, such as ketorolac, have been used successfully as postoperative analgesics in adults, either alone or in combination with opioids (Brown, Wild, & Bynum, 1988; Buckley & Brogden, 1990; Fragden & O'Hara, 1987; Frick & Angelocci, 1987; Gillies, Kenny, Bullingham, & McArdle, 1987; Keenan, Caver,

Langdon, & Lea, 1983; Maltila, Ahlstrong-Bengs, & Pekkola, 1983; Manifold, Champion, & Goepe, 1983; O'Hara, Fragen, Kinzer, & Pemberton, 1987; Rigmonti, Zanella, Lanpugnani, Marrano, Campione, Bruni, Mandelli, & Sacchetti, 1983; Yee, Bradley, Stanski, & Cherry, 1986; Yee, Brown, Sevelius, & Wild, 1984; Yee, Koshiver, Allbon, & Brown, 1986). At the present time, limited data exist on the use of NSAID's for postoperative pain control in children or on the use of combinations of opioid and non-opioid analgesics in children (Bean, Hunt, Coffield, Brindley, Verheyden, Brindley, Jr., & Custer, 1992; Bone & Fell, 1988; Watcha, Jones, Lagueruela, Schweiger, & White, 1992a; Watcha, Ramirez-Ruiz, White, Jones, Lagueruela, & Terkonda, 1992b; Watters, Patterson, Mathews, & Campbell, 1988).

In addition to determining analgesic efficacy, the measurement of drug-induced side-effects clearly plays a vital role in the overall assessment of any pharmacological agent. Concerns about side-effects often impact on prescriptive and administration practices which may result in undertreatment of the patient. Non-steroidal anti-inflammatory drugs may afford certain advantages as analgesics because of the low incidence of central nervous system side-effects. However, concerns have been raised about the potential impact of NSAID's on postoperative bleeding, especially with procedures such as tonsillectomy and adenoidectomy, which are associated with a risk of bleeding in the immediate postoperative period. Therefore, the incidence and severity of bleeding associated with the administration of a NSAID at the

completion of surgery, needs to be examined in children to assure that the benefits of the drug in the management of postoperative pain in children are not negated by side-effects.

Hence, this study was designed to examine the analgesic efficacy of postoperative administration of fentanyl with children following tonsillectomy, to determine whether administration of ketorolac at the completion of surgery enhanced the efficacy of fentanyl in relieving postoperative pain, and to determine if the administration of ketorolac increased the severity of postoperative bleeding in children following tonsillectomy.

STUDY PURPOSE

The purpose of this double blind, randomized clinical trial (RCT), in children following tonsillectomy with or without adenoidectomy, was to compare the analgesic requirements, postoperative pain intensity scores, the severity and duration of bleeding, and length of stay between children who received a single intramuscular (IM) dose of normal saline at the completion of surgery (saline group) and children who received a single IM dose of ketorolac at the completion of surgery (ketorolac group).

Specific Aims

The following specific aims were evaluated in a population of children recovering from tonsillectomy, with or without adenoidectomy or myringotomy, in an ambulatory surgery setting:

1. To determine the effect of a single IM dose of ketorolac, administered at

the completion of surgery, on the amount of opioid administered postoperatively.

2. To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on children's postoperative pain intensity scores.

3. To determine the effect of intermittent intravenous (IV) postoperative administration of fentanyl on pain intensity scores in the PACU, for children in the saline group and for children in the ketorolac group.

4. To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on the prevalence and severity of postoperative bleeding.

5. To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on the child's length of stay following surgery.

Assumptions

The assumptions underlying this study were as follows:

1. Children are capable of experiencing pain.
2. A surgical intervention causes pain in children.
3. Children are capable of communicating pain intensity through self-report.

Definition of Terms

For the purpose of this study, the following definitions were used:

1. Child. A male or female patient, age 3 to 12 years.
2. Tonsillectomy with or without adenoidectomy. An outpatient surgical

procedure requiring general anesthesia in which the tonsil, or tonsil and adenoid tissues, are dissected and removed.

3. Postoperative pain intensity scores. Scores of pain intensity determined by a self-report measure and a behavioral rating scale.

a. Self-report of pain intensity. Quantification of the child's perception of the amount of pain that he or she is presently experiencing, using either the photographic or numeric scales of the Oucher (Beyer, 1984).

b. Behavioral pain intensity. Quantification of the child's pain intensity based on his or her behaviors, using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath, Goodman, Schillinger, Dunn, & Chapman, 1985).

4. Analgesic requirements. The amount of opioid administered postoperatively.

5. Duration of postoperative bleeding. The length of time following surgery required for postoperative bleeding to completely resolve.

6. Severity of postoperative bleeding. Quantification of the amount of postoperative hemorrhage using a four-level grading scale adapted from Guida and Mattucci (1990).

7. Intramuscular dose of saline. IM injection of 1 cc of normal saline into the child's deltoid muscle at the completion of surgery.

8. Intramuscular dose of ketorolac. IM injection of ketorolac (1 mg/kg) into the child's deltoid muscle at the completion of surgery.

9. Completion of surgery. The time immediately following conclusion of the surgical procedure and preceding the termination of general anesthesia.

10. Post-operative. Period of time after surgery, from arrival in the Post-Anesthesia Care Unit (PACU) to discharge from the hospital on the day of surgery.

11. Ambulatory surgery setting. An extension of surgery, in which elective operative procedures are performed under general anesthesia, and patients are admitted to and discharged from the hospital on the same day.

12. Opioid analgesic. Drugs with opium- or morphine-like properties, employed primarily to relieve pain.

CHAPTER 2

LITERATURE REVIEW

The review of the literature focuses on several topics of particular relevance to this study. First, the etiology of postoperative pain is presented, with an emphasis on specific pain mechanisms associated with tonsillectomy, with or without adenoidectomy. Second, the basic mechanism of action of opioid agonists is discussed, followed by a review of the studies on the pharmacokinetics, pharmacodynamics, and efficacy of fentanyl in the management of pain in children. Data on the pharmacokinetics and pharmacodynamics of ketorolac are also presented. Finally, clinical studies that examined the use of ketorolac as an analgesic in the management of postoperative pain in children, and it's associated side-effects, are reviewed.

Mechanisms of Postoperative Pain Following Tonsillectomy With or Without Adenoidectomy

The pathophysiologic mechanisms involved in acute surgical pain are extremely complex. Three major types of pain have been described as contributing to the post-operative pain experience including: cutaneous pain, deep somatic pain, and visceral pain (Benedetti, Bonica, & Bellucci, 1984; Bonica, 1990). Pain following adenotonsillectomy results from surgical dissection and operative trauma to surrounding tissues, with subsequent inflammation, ischemia, irritation of sensory nerve endings and spasm of the pharyngeal muscles (Rundle, 1967; Slassa, Seaman, Ruff, Lenis, Bellins, &

Brown, 1988; Talbot, 1965).

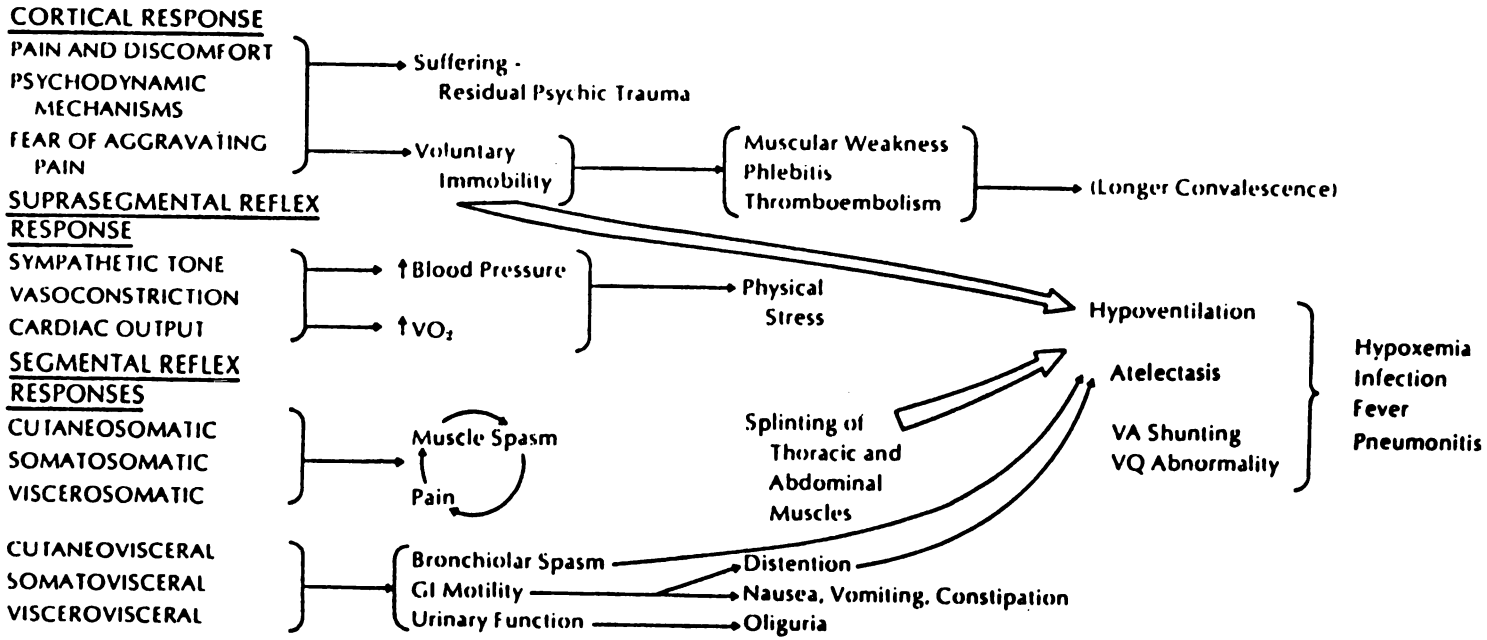
Primary afferent neurons, with peripheral terminals that respond differentially to noxious stimuli, are widely distributed throughout the skin and internal tissues (Fields, 1987). Cutaneous pain can result from severed or damaged nerves, although it is more often a physiologic process which is mediated by the release of chemical substances (e.g., potassium ions, hydrogen ions, bradykinin, serotonin, substance P, lactic acid, histamine, and prostaglandins) which cause inflammation and sensitization of nociceptors (Zimmermann, 1979). Sensitization is manifested by a reduction in the firing threshold of nociceptors (Perl, 1976), causing them to be activated by non-noxious stimuli; an exaggerated response to noxious injury; and spontaneous activity or firing of the nociceptor (Meyer & Campbell, 1981). The characteristics of cutaneous pain are described as well-localized, sharp in quality, and often associated with a burning sensation (Benedetti et al., 1984).

Deep somatic pain results from acute damage to nerves in fascia, muscle, pleura, peritoneum, or periosteum following surgical intervention. It is characterized as being a diffuse, aching sensation (Benedetti et al., 1984). Major surgical procedures are likely to generate stimuli from multiple somatic tissues, such as those identified above, and make an additional contribution to the postoperative pain experience. Nociceptors in visceral organs respond somewhat differently to stimulation than those associated with surface tissues.

Figure 1 - The pathophysiology of postoperative pain.

From Bonica, J. J., & Benedetti, C. (1980). Postoperative Pain. In R. E. Condon & J. J. DeCosse (Eds.), Surgical care: A physiological approach to clinical management (pp. 394-415), Philadelphia: Lea & Febiger.

PHYSIOPATHOLOGY OF POSTOPERATIVE PAIN



Operative stimuli which have the potential to elicit visceral pain include: irritation of the mucosal and serosal surfaces; extensive manipulation of the mesentery; stretching or distention of a hollow viscus; and spasm of the smooth muscles of the cardiovascular, respiratory, gastrointestinal and genitourinary systems (Leek, 1972; Benedetti et al., 1984). The quality of visceral pain is described as being deep and achy, or colicky (Payne, 1989).

An additional factor which contributes to postoperative pain is the activation of segmental reflexes which are triggered by nociceptive input from the area of tissue damage. For example, segmental peripheral vasoconstriction following activation of ventral horn motor neurons, causes ischemia and eventual acidosis, resulting in the development of muscle tension which culminates in muscle spasm (Benedetti, 1990). For children following adenotonsillectomy, the relative immobility of the pharynx causes muscular spasm in the pharyngeal muscles. Swallowing produces more pain, which results in a reluctance to swallow, causing more muscle spasms and therefore more pain (Valijan, 1989).

Pharmacologic Management of Postoperative Pain in Children Following Tonsillectomy, With or Without Adenoidectomy

The need for analgesics depends upon the nature of the surgery and the pain threshold and response of the patient. Following adenotonsillectomy, pain management in children relies primarily on pharmacologic treatment with opioid analgesics, especially in the immediate postoperative period.

Most of the published experience with fentanyl in pediatrics has been in the

area of induction and maintenance of anesthesia, generally combined with other anesthetic agents. Recent clinical experience suggests that intermittent intravenous injection of fentanyl may be a useful approach to the management of pain following tonsillectomy and/or adenoidectomy for children in the initial postoperative period. However, systematic studies have not been done to evaluate the efficacy of intravenous bolus administration of fentanyl in providing postoperative analgesia for children.

Mechanisms of Opioid-Induced Analgesia

Opioid analgesics are the most commonly used pharmacologic agents for the control of moderate to severe post-operative pain in children (Berde, 1989; Shannon & Berde, 1989). The pure agonists (e.g., morphine) are the drugs of choice in pediatrics primarily because there is limited experience using mixed agonist/antagonists in this population (Lynn, 1990). The mechanism of action of pure agonists entails complex interactions with stereospecific receptors distributed at several different sites within the central nervous system and the periphery. Multiple opioid receptors have been identified including: mu, kappa, delta, and sigma. Specific pharmacologic effects have been reported for each class of receptor (Benedetti, 1990; Jaffe & Martin, 1985) and are summarized in Table 1.

Opioid binding sites are distributed in the limbic system, thalamus, striatum, hypothalamus, midbrain, and spinal cord (Atweh & Kuhar, 1983; Faull & Villager, 1987; Gouarderes & Cros, 1984; Gouarderes, Cros, & Quirion, 1985;

Sales, Charnay, Zajac, Dubois, & Roques, 1989; Zarr, Werling, Brown, & Cox, 1986) as well as in the periphery (North & Egan, 1983). The acute effects of opioids include: a reduction in neurotransmitter release from the terminals of nerves carrying nociceptive stimuli (Duggan & North, 1983); inhibition of neuronal electrophysiologic activity (Way, 1986); and activation of descending antinociceptive systems. This activation of descending control systems is believed to be the major mechanism of analgesia following administration of therapeutic doses of oral, intramuscular (IM), and intravenous (IV) opioids (Benedetti, 1990). Alteration in the emotional response to pain (e.g., patients perceive the pain to be more bearable) is attributed to the direct action of opioids on the limbic system (Benedetti, 1979).

Pharmacodynamics and Pharmacokinetics of Fentanyl in Children

Fentanyl is a synthetic opioid and has approximately 100 times the analgesic potency of morphine (Yaster & Deshpande, 1988). Fentanyl exerts its effect at the mu-receptor (Jaffe & Martin, 1985). Following intravenous administration, fentanyl is widely distributed to highly perfused organs and tissues (Mather, 1983). The onset of fentanyl's analgesic effect, following intravenous administration, is almost immediate and peak analgesic effect occurs within 3 to 5 minutes (Schachtel, 1992). Fentanyl has a high lipid solubility and is removed from the plasma rapidly due to its extensive uptake by body tissues (McClain & Hug, 1980). The duration of action of fentanyl is approximately 30 to 60 minutes and is limited by redistribution within the body

Table 1

Summary of the Pharmacological Effects Associated with Specific Opioid Receptors

Receptor Types	Pharmacologic Effects
μ	Supraspinal analgesia, respiratory depression, euphoria, nausea and vomiting, constipation, and physical dependence
κ	spinal analgesia, miosis, and sedation
δ	analgesia
θ	dysphoria, hallucinations, and respiratory and vasomotor stimulation

(Physician's Desk Reference, 1992). Metabolism and elimination is almost exclusively hepatic (Mather, 1983; McClain & Hug, 1980). The recommended analgesic dose range of fentanyl for intravenous bolus administration in children is 0.5-2.0 micrograms/kilogram of body weight, titrated to the desired analgesic effect (Schachtel, 1992).

Fentanyl's dose and route of administration will determine the rate of entry of the drug into the plasma and ultimately the maximum analgesic response that is produced (Boas, Holford, & Villiger, 1985). Bolus administration of an opioid analgesic, such as fentanyl, is capable of producing high initial peak concentrations and potentially toxic concentrations, followed by rapid decline of levels to a sub-therapeutic range (Koren & Maurice, 1989). Since optimum analgesia and the appearance of side-effects are most likely to occur during the period of peak plasma concentration, measures of analgesic efficacy and toxicity should be obtained during the period of maximum drug effect.

Information on the pharmacology of fentanyl in pediatrics remains sparse. Much of the data, supporting the clinical use of fentanyl in children, are extrapolated from adult studies. Published pharmacokinetic studies of fentanyl in children are limited (Johnson, Erickson, Holley, & Scott, 1984; Singleton, Rosen, & Fisher, 1987; Koehntop, Rodman, Brundage, Hegland, & Buckley, 1986). These studies do not provide appropriate data for extrapolating dosing and administration recommendations for the use of fentanyl as an analgesic, since the studies (Johnson et al., 1984; Singleton et al., 1987; Koehntop et al,

1986) have evaluated the use of high-dose fentanyl as an anesthetic agent in children. Pharmacokinetic studies, in children receiving fentanyl for postoperative pain management, have not been reported.

Age-related differences in the pharmacokinetic profile of high-dose fentanyl have been described between newborn infants, children, and adults. The most notable differences exist in the pharmacokinetic parameters of clearance, steady state volume of distribution, central compartment volume, and distribution half-life. Compared with adults, infants and children have a larger central volume of distribution, a larger steady-state volume of distribution, and a longer distribution half-life (Johnson et al., 1984; Singleton et al., 1987; Koehntop et al, 1986). Infants have the fastest drug clearance rates, whereas the values reported for children begin to approach those cited for adults. Given the limited available data, the findings of these studies suggest an inverse relationship between age and each of these parameters. Pharmacokinetic differences that are believed to result from changes in developmental physiology are reported to be greatest during the neonatal period.

The implications of these age-related pharmacokinetic differences include a potential for lower plasma fentanyl concentrations in infants and children with the same microgram/kilogram dose. Singleton and colleagues (1987) showed lower plasma fentanyl concentrations in infants compared to children or adults following comparable doses per kilogram. In addition, the longer distribution half-life coupled with a prolonged elimination half-life, may contribute to

accumulation of fentanyl if repeated doses are given for maintenance of analgesia.

Clinical Studies in Children Receiving Fentanyl for the Control of Postoperative Pain

Studies have not been done to evaluate the efficacy of IV bolus administration of fentanyl in providing postoperative analgesia for children. Data are limited to clinical evaluations of oral transmucosal fentanyl citrate (OTFC) for preoperative sedation (Ashburn, Streisand, Tarver, Mears, Mulder, Floet Wilms, Luijendijk, Elwyn, Pace, & Stanley, 1990; Feld, Champeau, van Steennis, & Scott, 1989; Friesen & Lockhart, 1992; Goldstein-Dresner, Davis, Kretchman, Siewers, Certo, & Cook, 1991; Nelson, Streisand, Mulder, Pace, & Stanley, 1989; Streisand, Stanley, Hague, van Vreeswijk, Ho, & Pace, 1989); reports of intravenous bolus administration of fentanyl used for sedation and analgesia for brief procedures (Billmire et al., 1985; Sandler et al., 1992; Yaster et al., 1990); intraoperative administration of fentanyl (Chen et al., 1991); the use of a continuous infusion of fentanyl in adolescents following surgery (Koren & Maurice, 1989); and a case report of intrathecal fentanyl administration in a child following inadvertent dural puncture during epidural catheter placement (Tobias, 1991).

Studies which have examined OTFC (Ashburn et al., 1990; Feld et al., 1989; Friesen & Lockhart, 1992; Goldstein-Dresner et al., 1991; Nelson et al., 1989; Streisand et al., 1989) have demonstrated a rapid onset of preoperative

sedation, anxiolysis, and facilitation of inhalation induction of anesthesia. One study (Ashburn et al., 1990) reported decreased analgesic requirements in the recovery room in those patients who received preoperative OTFC (10-15 micrograms/kilogram) compared to placebo.

Bilmire and colleagues (1985) reported on the use of fentanyl in the outpatient treatment of 2,000 pediatric patients requiring repair of facial trauma. Dosages ranged from 2 to 3 mcg/kg given slow IV push over 3 to 5 minutes. Although no formal analgesic measure was reported, anecdotal reports suggested that fentanyl was useful in reducing procedure-related pain.

Other investigators (Sandler et al., 1992) have reported the use of fentanyl in conjunction with local anesthetics and other sedatives, as pre-medication for painful procedures (e.g., lumbar puncture and bone marrow aspiration) in 25 pediatric oncology patients. A maximum dose of 4 mcg/kg, diluted in normal saline, was given IV over 10 minutes. The dose administered was titrated to the patient's response. Patients reported no change in pain relief, using a faces scale (Whaley & Wong, 1979), when fentanyl was added to the premedication regime for the procedures. Parents reported an improvement in their child's response following fentanyl administration.

Koren and Maurice (1989) have reported on their clinical experience with the use of a continuous fentanyl infusion in 12 adolescents following surgery. All patients received a loading dose of 3.5 mcg/kg over 30 to 50 minutes, followed by a continuous infusion of 1-2 mcg/kg/hour. Good pain control was

reported for all of the adolescents, although no formal pain measure was used.

Chen and colleagues (1992) conducted a study, reported in abstract, that compared the effects of intraoperative ilioinguinal/iliohypogastric (IG/IH) nerve block to IV fentanyl for postoperative pain control following inguinal herniorrhaphy in pediatric outpatients. Seventy-five children (aged 1 to 10 years), with unilateral inguinal herniorrhaphy, were randomly divided to receive one of the following treatments immediately after induction: IG/IH nerve block using 0.25% bupivicaine (1 mg/kg); IV fentanyl (1 mcg/kg); or general anesthesia alone (control group). Pain was measured using a modified Hannallah's scoring system after the patient was fully awake in the post-anesthesia care unit (PACU). Parents were also contacted, by telephone, 24 hours after discharge, to assess the prevalence of vomiting, drowsiness, pain, and shivering at home. Children in the fentanyl group had lower pain scores than the nerve block group for the first 30 minutes in the PACU. However, recovery time (evaluated using Steward's scoring system) was longer in children who received fentanyl. Children who received either the IG/IH nerve block or IV fentanyl had lower pain scores than children in the control group. Statistical significance for these findings were not reported. There were no significant differences among groups as, reported by the parents, regarding the prevalence of vomiting, drowsiness, pain, and shivering at home.

Tobias (1991) published a case report on the use of an intrathecal fentanyl infusion (0.2 mcg/kg/hour), following inadvertent dural puncture during epidural

placement for an orthopedic surgical procedure. The child was reported to be awake and comfortable, although no formal analgesic measure was used. No supplemental analgesic agents were required during intrathecal fentanyl administration.

Pharmacodynamics and Pharmacokinetics of Ketorolac in Children

Ketorolac tromethamine (Toradol, Syntex) is the first injectable non-steroidal anti-inflammatory drug (NSAID) approved for the management of acute pain. Ketorolac is a potent analgesic with both analgesic and anti-inflammatory properties and is recommended for the short-term management of moderate to severe pain. Although the exact mechanism of action is not known, its effects appear to be peripherally mediated by inhibition of prostaglandin synthesis, through blockade of the cyclooxygenase pathway.

When the cell membrane is damaged, as during tissue injury, arachidonic acid is released by a membrane-bound phospholipase enzyme. Catalyzed by the enzyme cyclooxygenase, arachidonic acid reacts to form various biologically active factors, including prostaglandins, prostacyclins, and thromboxanes. Although prostaglandins have many functions, they contribute to the development of hyperalgesia at the site of tissue injury by sensitizing nociceptive receptors to various chemical, mechanical, and thermal stimuli (Kandel & Schwartz, 1985). NSAIDS, such as ketorolac, are believed to alleviate pain by inhibiting cyclooxygenase, thereby lowering levels of prostaglandins at peripheral pain receptors.

Following intramuscular administration of ketorolac, in adults, onset of analgesia is reported to occur within 10 minutes (Jay, 1991), peak analgesia occurs within 75 to 150 minutes (Dipalma, 1991; Estenne, Julien, Charleux, Arsac, Arvis, & Loygue, 1988; O'Hara, Fragen, Kinzer, et al., 1987; Yee, Koshiver, Allbon, et al., 1986), and the duration of effect lasts approximately 6 to 8 hours (Estenne et al., 1988; O'Hara et al., 1987; Yee et al., 1986). Comparable pharmacokinetic studies have not been conducted in children.

The pharmacokinetics of a single postoperative, intravenous dose of ketorolac (0.5 mg/kg) was reported for 10 children, ages 4 to 8, following strabismus surgery (Olkkola & Maunuksela, 1991). Data from this study suggest that clearance (Cl) and steady-state volume of distribution (V_{ss}) were approximately two times higher in children than the values reported for adults (Jung, Mroszczak, & Bynum, 1988; Mroszczak, Lee, Combs, Sarnquits, Huang, Wu, Tokes, Maddox, & Cho, 1987). However, elimination half-life ($t_{1/2}$) was similar to that reported for adults (Mroszczak et al., 1987).

Clinical Studies in Children Receiving Ketorolac for the Control of Postoperative Pain

In single-dose studies, intramuscular administration of ketorolac compared favorably to opioids in the management of moderate to severe postoperative pain in adults (Buckley & Brogden, 1990). While recent clinical experience suggests that a single dose of ketorolac is efficacious in reducing acute pain in children, there are only three reports of randomized, placebo-controlled trials of

ketorolac administration in children (Bean et al., 1992; Watcha et al., 1992a; Watcha et al., 1992b).

Bean and colleagues (1992), conducted a study, reported in abstract, with 40 children, 1 to 10 years of age, undergoing surgery which normally required perioperative narcotics (the specific procedures were not identified). Children were randomized into 1 of 3 treatment groups: IM ketorolac (0.75 mg/kg; N=14), IM meperidine (1 mg/kg; N=12), and normal saline (N=14). The study drug was administered following a standardized inhalation induction. Duration of surgery ranged from 54 to 122 minutes. Pain scores were recorded in the PACU using the CHEOPS at intervals of 5, 10, 15, 30, 45, 60, and 120 minutes. Additional doses of meperidine (0.5 mg/kg) were given for CHEOPS score of $\geq$ 9. At 10 minutes postoperatively, median pain scores were reported to be 7 for children in the ketorolac group, 6 for children in the meperidine group, and 10 for children in the placebo group. No statistical analyses were reported. Pain scores were comparable and less than 8 for all 3 groups at 60 and 120 minutes postoperatively. The pain intensity scores for the other time intervals were not reported.

All patients in the saline group (14/14) required supplemental narcotics, as did 57% (8/14) of the children in the ketorolac group and 42% (5/12) of the children in the meperidine group. Children in the saline group received a total of 33 additional doses of meperidine in the PACU. While children in the ketorolac group and children in the meperidine group received 16 and 8

additional doses of meperidine, respectively.

The authors concluded that IM administration of ketorolac (0.75 mg/kg) provided postoperative analgesia comparable to meperidine (1 mg/kg). However, 57% of the children in the ketorolac group received supplemental doses of meperidine, and received twice as many opioid analgesic doses as the meperidine group. The absence of reported statistical analyses contributes to the difficulty in interpreting these findings. Pain intensity scores were not evaluated in relationship to the onset of action of the study drugs. The sample size is small, and the homogeneity of the sample across groups is not reported, precluding any definitive conclusions about these results.

Watcha and colleagues (1992a) reported a double-blind, placebo-controlled study of 95 children (ages 5 to 15 years), undergoing tonsillectomy, orthopedic, and plastic surgery procedures. Children were randomized into one of three treatment groups: IV ketorolac (0.9 mg/kg), IV morphine (0.1 mg/kg), and IV normal saline. The study drug was given after induction prior to the surgical incision. The mean duration of surgery was 45 minutes (S.D.=32) for the ketorolac group, 48 minutes (S.D.=37) for the morphine group, and 53 minutes (S.D.=50) for the placebo group. There were no differences between the 3 groups with respect to age, weight, ASA physical status, anesthetic technique, type of surgery, and duration of surgery and anesthesia.

Pain was measured in the PACU at 10 to 15 minute intervals by the patient self-report using a 0-100 visual analogue scale (VAS) and by an observer,

using an objective pain scale (OPS) (Hannallah, Broadman, Belman, Abramowitz, & Epstein, 1987; Broadman, Rice, & Hannallah, 1988). There were no significant differences among the pain scores for the three treatment groups within 5 minutes after arriving in PACU. Ten minutes after arrival in the PACU, mean VAS and median OPS scores were significantly lower ($p < 0.05$) in both the morphine and ketorolac groups compared to the placebo group. By 30 minutes, all patients in moderate-to-severe pain had received supplemental morphine, and there were no differences in VAS or OPS scores among the three groups. Pain intensity scores were only reported for the PACU.

At 12 minutes following arrival in the PACU, the percentage of children in each treatment group who received supplemental opioids was determined. No rationale for the 12 minute cut-off was stated. A significantly larger percentage of the children in the saline group ($p<0.05$) received supplemental doses of morphine than either the morphine or ketorolac group. In addition, the authors report that in all three groups, children undergoing orthopedic procedures required more doses of supplemental opioid analgesics, than those children undergoing tonsillectomy. However, whether the number of doses were significantly different was not reported.

The median number of doses of analgesics administered at 6 and 24 hours following discharge from the PACU, was statistically significantly higher in the placebo group compared to either the ketorolac or the morphine group ($p<0.05$). Total doses of opioids administered were not reported. These data suggest

that intraoperative IV administration of a single dose of ketorolac (0.75 mg/kg) does not eliminate the need for supplemental opioid analgesics, although it may decrease the amount of additional opioid required to provide postoperative pain relief in children. This lack of analgesic effect may relate to the dose of ketorolac used in this study (which may be sub-therapeutic), or the timing of administration of the drug, which would impact peak analgesic effect.

A double-blind, placebo-controlled study was done to compare the postoperative analgesic and side-effect profiles of oral administration of acetaminophen or ketorolac (Watcha et al., 1992b) in children undergoing bilateral myringotomy tube (BMT) placement. Children (mean age=2.6 years, S.D.=2.3 years) were randomized into one of the following groups: a saline group (N=29), an acetaminophen group (10 mg/kg; N=31), or a ketorolac group (1 mg/kg; N=30), and received the study drug 30 minutes prior to induction. The duration of surgery was 7.5 minutes (S.D.=4.7) for the saline group, 7.2 minutes (S.D.=4.9) for the acetaminophen group, and 6.9 minutes (S.D.=3.5) for the ketorolac group. The child's pain intensity was scored using an objective pain scale (OPS; Hannallah, Broadman, Belman, Abramowitz, & Epstein, 1987), with measures recorded on arrival in the PACU, at 1 and 5 minutes following arrival, and then at 5 minute intervals. Additional items that were scored included the times from arrival in the PACU to eye opening, oral intake, ambulation, "home readiness," and time to response to verbal commands (when age appropriate). Parents were permitted in the PACU, and the behavior of the

child before and after the arrival of a family member was measured using a 4-point scale (1=calm, quiet; 2=crying, but can be consoled; 3=crying, cannot be consoled, and 4=agitated and thrashing around). The OPS scores were significantly lower in the ketorolac group than in the acetaminophen and placebo groups, at 1, 5, 10, and 15 minutes after arrival in the PACU, irrespective of the presence or absence of the parent (Kruskal-Wallis test; $p<0.05$). Only the OPS scores prior to rescue analgesic administration were included in the statistical analyses.

The percentage of children requiring supplemental analgesics was reported at 10, 15, 20, 30, 40, 50, and 60 minutes following arrival in the PACU. Statistically significant decreases in the percentage of children requiring supplemental analgesics in the ketorolac group compared to the saline group were seen from 20 to 60 minutes postoperatively ($p<0.05$). However, the percentage of children in the acetaminophen group and the saline group were not significantly different. Statistical comparisons of the total dose of analgesics administered in the acetaminophen and ketorolac groups were not reported.

The authors conclude that oral administration of ketorolac (1 mg/kg) provided more effective analgesia than either acetaminophen (10 mg/kg) or saline, in children undergoing BMT. Further study is needed to determine whether higher doses of acetaminophen would be more effective in this patient population, and to determine the efficacy of oral ketorolac for more painful ambulatory surgical procedures.

The Effect of Ketorolac on Postoperative Bleeding in Children

The potential for an increased risk of bleeding is especially pertinent when considering the use of ketorolac with surgical procedures such as tonsillectomy, with or without adenoidectomy, which carry a significant surgical risk for bleeding. Studies in healthy adults using ketorolac have demonstrated an increase in bleeding times (Conrad Fagan, Mackie, & Mayshar, 1988; Greer, 1990; Roe et al., 1981; Spowart, Greer, McLaren, Lloyd, Bullingham, & Forbes, 1988), although most values remained within normal limits. In addition, most of these studies evaluated multiple-doses and/or combined routes of administration of ketorolac. No significant effects on platelet count, prothrombin time (PT), or partial thromboplastin time (PTT) have been reported.

Of the 3 studies which have investigated the use of ketorolac in children (Bean et al., 1992; Watcha et al., 1992a; Watcha et al., 1992b) only 2 of the studies have reported on the effect of ketorolac on postoperative bleeding. Bean and colleagues (1992) obtained bleeding times in children following induction and again 180 minutes after administration of the treatment drug (i.e., ketorolac, morphine, or placebo). Bleeding time, for children receiving ketorolac, was slightly increased from 186 $\pm$ 71 (at the time of induction) to 242 $\pm$ 91 (after treatment; $p=0.04$), but did not exceed normal limits in any patient. No clinically significant postoperative bleeding was reported.

In the study conducted by Watcha and colleagues (1992a), 63 of the 95 children participating underwent tonsillectomy-adenoidectomy procedures.

Postoperative bleeding was not evaluated specifically, but anecdotal comments suggest that there was no clinically significant postoperative bleeding. Only one child, in the saline group, had to return to the operating room for excessive bleeding on the fifth postoperative day, which is well beyond the time required for complete elimination of the study drugs.

Summary

Many assumptions are made about the severity, duration, and type of pain experienced by children following surgery. However, there is little objective data available on the prevalence and severity of postoperative pain in children following tonsillectomy.

In addition, limited data exist on the use of fentanyl, as an analgesic agent in children. To date, no studies have evaluated the analgesic efficacy of bolus intravenous fentanyl administration in children following surgery. While the addition of an NSAID, like ketorolac, to the perioperative pain management plan, may result in an enhanced analgesic effect, there have been only two placebo-controlled studies in children to evaluate the efficacy and safety of an intramuscular injection of ketorolac at the beginning of surgery on the management of postoperative pain in children. The effect of ketorolac on hemostasis and postoperative bleeding has only been examined in one study investigating intramuscular administration of the drug, and in one study investigating intravenous administration of ketorolac.

The review of literature supports the need for further data on the prevalence

and severity of postoperative pain in children and the efficacy of fentanyl as a postoperative analgesic, as well as the efficacy of ketorolac in enhancing the effectiveness of opioid analgesics without increased risk of bleeding. These data would provide direction for new strategies that would optimize the management of postoperative pain in children.

CHAPTER 3

METHODOLOGY

Research Design

The purpose of this single blind, randomized clinical trial (RCT), in children following tonsillectomy with or without adenoidectomy, was to compare the postoperative pain intensity scores, analgesic requirements, length of stay, and the severity and duration of bleeding between children who received a single intramuscular (IM) dose of normal saline at the completion of surgery (saline group) and children who received a single IM dose of ketorolac at the completion of surgery (ketorolac group).

Research Setting

The study was conducted in a 182-bed private, non-profit children's hospital servicing 10 counties in a 60,000 square mile area of central California. The ambulatory surgery program is integrated into the existing inpatient surgical program, utilizing existing inpatient operating rooms, as well as admitting, and pre- and post-operative areas. A 6-bed room is used for observation of patients from the ambulatory surgery program, once they are discharged from the PACU. Approximately 5,200 children are admitted annually through the Ambulatory Surgery Program for various outpatient procedures. Of these, about 9% are admitted for tonsillectomy, with or without adenoidectomy (Valley Children's Hospital, 1992).

Sample

Participants were children ages 3 to 12 years who were admitted to Ambulatory Surgery for tonsillectomy, with or without adenoidectomy. Children were selected based on the following criteria:

1. Admission to Day Surgery for tonsillectomy, with or without adenoidectomy.
2. Parental consent for the child to participate in the study.
3. Child assent to participate in the study.
4. No prior history of neurological impairments (i.e., visual or hearing deficits, learning disability, or motor function deficit).
5. Patients with no known allergies to opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDS).
6. Patients with no history of a bleeding disorder.
7. Patients who were English speaking.
8. Patients who received intravenous fentanyl by bolus administration for postoperative pain management.

Variables and Instruments

The variables of interest and the instruments used to measure them are summarized in Table 2.

Table 2

Data Collection Methods/Instruments

Variables	Instruments	Empirical Referent
Pain Intensity		
Self Report Scale		
	Oucher (Beyer, 1984)	A poster-like instrument with a 0 to 100 numerical scale (interval data) on the left for older children and a series of 6 photographs depicting increasing amounts of pain (ordinal data) on the right for younger children, scored 0 to 5
Behavioral Observation Scale	CHEOPS (McGrath et al., 1985)	Raters provide a score for a child's behaviors on the basis of observations made in 6 specific areas: cry, facial and verbal responses, and movement in the arms, legs and torso; Scores range from 4 to 13
Duration of Postoperative Bleeding		The total length of time (in minutes) required for postoperative bleeding to completely resolve
Severity of Postoperative Bleeding	Grading Scale for Postoperative Bleeding (adapted from Guida and Mattucci, 1990).	Scores range from 0 to 3, describing increased amounts of bleeding that require more aggressive intervention
Amount of opioid analgesic administered postoperatively		The total microgram dose of fentanyl administered postoperatively

Demographic Questionnaires

Patient/Family Information Sheet - Appendix A

Description: The patient/family information sheet is a 16-item questionnaire designed to obtain the following demographic data: number of siblings, birth order, indication for surgery, most recent episode of tonsillitis, history of bleeding problems, medication allergies, parental educational backgrounds and ethnicity, household income, family history of pain problems, the child's most painful experience, parental assessment of child's ability to cope with pain, and previous history of hospitalization or surgery.

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

Method of Administration: The patient/family information sheet was completed by the parent(s) once consent to participate in the study was obtained. The form was returned to the investigator before the child was taken to surgery.

Scoring: Information was summarized using appropriate descriptive statistics.

Medical Record Review Form - Appendix B

Description: The medical record review form is a 43 item data collection form designed to obtain the following demographic data: the child's medical record number, date of birth, age, weight, sex, ASA level, type of surgical procedure, indication for surgery, surgeon, anesthesiologist, preoperative lab

values, vital signs, level of sedation, type of anesthesia, intraoperative medications, length of anesthesia and surgery, estimated blood loss, and surgical and hemostasis techniques.

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

Method of Administration: The medical record review form was completed by the investigator through a review of the chart and operative report at the completion of the child's surgical procedure.

The study drug administered was coded by number on the operative record, so that the investigator remained blinded during the chart review.

Scoring: Information was summarized using appropriate descriptive statistics.

Pain Intensity Measures

The Oucher - Appendix C

Description: The Oucher (Beyer, 1984) is a self-report rating scale, used to measure pain intensity in children ages 3 to 12 years, which has been used with postoperative pediatric patients. It is a poster type instrument with 2 scales. The vertical numeric scale on the left ranges from 0 (no hurt) to 100 (the biggest hurt you could ever have), and requires that children be able to count from 0 to 100. The photographic scale on the right is used with younger children and consists of a series of 6 photographs of the face of the same preschool child arranged vertically from "no hurt" to "the biggest hurt you could

ever have."

Validity and Reliability: A series of methodological studies have reported strong support for the content, convergent, discriminant, and construct validity of the OUCHER as a measure of pain intensity in 3 to 12 year old children (Aradine, Beyer, & Tompkins, 1988; Belter, McIntosh, Finch, & Saylor, 1988; Beyer & Aradine, 1986, 1987, 1988; Hawley, 1984). Moderate support for test-retest reliability assessed indirectly was provided by Belter and colleagues (1988).

Method of Administration

Determination of Appropriate Scale. If the child was 8 years of age or older, and able to count to 100, they were instructed in the use of the numeric scale; if not, the photographic scale was used.

Introduction of the Oucher. Prior to surgery, the Oucher was introduced as a way to help children tell us how much hurt they have. The explanation of the OUCHER provided to a younger child was as follows: "This is my poster called the 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 a lot of hurt (pointing to the fourth picture). This one shows a real 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)."

When the OUCHER was used with an older child, the numerical scale was 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 hurts; if your hurt is somewhere in here (pointing to the middle third of the scale between 30-69), it means you have medium or a middle amount of hurt; if your hurt is somewhere in here (pointing to the upper third of the scale between 70-99), it means you have big hurts. If you point to 100, it means you have the biggest or worst hurt you could ever imagine." The children were told they could use any number between 0 and 100, not just the numbers shown on the Oucher poster. The child was given an opportunity to practice using the scale by rating pain intensity associated with recent lab work or alternate sample scenarios.

Postoperative Measures. Following surgery, the Oucher was used to obtain measures of the child's self report of pain intensity. After re-explaining the scale, the child was asked to select the number or picture from the poster in response to the question: "How much hurt do you have right now?" Pre- and post-drug measures were obtained, as well as hourly measures until the time of discharge.

Scoring. If the child used the numeric scale, the number he/she gave was the Oucher score. If the child used the photographic scale, their picture selections were converted to scores ranging from 0 to 5. The bottom picture was scored as 0, the second picture was scored as 1, the third picture was

scored as 2, the fourth picture was scored as 3, the fifth picture was scored as 4, and the sixth picture was scored as 5. The numeric score was treated as interval data and the photographic score was treated as ordinal data.

The CHEOPS - Appendix D

Description: The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS; McGrath et al., 1985), is a behavioral observation measure, which has also been used as a measure of pain in children following surgery. It was originally developed to measure postoperative pain in children aged 1 to 7. Six categories of behaviors (cry, facial, verbal, torso, touch, and legs) are observed with this measure.

Validity and Reliability: Inter-rater reliability and validity have been demonstrated during the development of the instrument on a sample of children emerging from anesthesia in the Post-Anesthesia Care Unit (PACU) (McGrath et al., 1985). However, recent studies have demonstrated a lack of correlation between the scores obtained from the CHEOPS and self-report scales, such that CHEOPS scores tended to underestimate pain intensity relative to the self-report measures (Beyer, McGrath, & Berde, 1990; Berde, Beyer, Bournaki, Levin, & Sethna, 1991).

Method of Administration: In this study, the CHEOPS scores were determined using a different time sampling method than was used in the original development of the instrument. Behaviors were observed for 5 seconds and then recorded by the investigator to obtain the CHEOPS score. A score

ranging between 4 and 13 was obtained for each observation-recording period. Children were observed for pain intensity both pre- and post-analgesic administration, as well as hourly until the time of discharge.

Scoring: The investigator scored the children's behaviors in 6 specific areas: cry, facial and verbal responses, and movement in the arms, legs, and torso. Each behavioral category was scored according to the following criteria: 0 = behavior that is the exact opposite of pain; 1 = behavior that is not indicative of pain and is not the exact opposite of pain; 2 = behavior indicating mild or moderate pain; 3 = behavior indicative of severe pain. The range of possible scores varies for each category (i.e., cry [1 to 3], facial [0 to 2], child verbal [0 to 2], torso [1 to 2], touch [1 to 2] and legs [1 to 2]). Using this scoring method, the range of a possible total score for each measurement time period was 4 to 13.

Grading Scale for Postoperative Bleeding - Appendix E

Definition: The 4-item grading scale for postoperative bleeding was adapted from Guida and Mattucci (1990) who utilized the scale to assess the incidence and severity of hemorrhage following tonsillectomy in children.

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

Method of Administration: The child was observed by the investigator for bleeding at the intervals outlined in the procedure. Any interventions for bleeding that were performed were recorded.

Scoring: The objective rating scale was scored according to the following criteria: Grade 0 = no observed bleeding; Grade 1 = mild bleeding which stopped spontaneously; Grade 2 = moderate bleeding requiring intervention (e.g., iced saline or phenylephrine hydrochloride (0.25%) nose drops); and Grade 3 = severe bleeding, necessitating either placement of a posterior nasal packing or the child's return to the operating room for hemostatic control (e.g., electrocautery).

Study Procedure

Children and their parents were approached to participate in the study prior to surgery on the morning of admission through the Day Surgery registration. Subject eligibility was based upon the previously stated criteria. Informed consent was obtained in accordance with the standards of the Committee for Human Research at the University of California, San Francisco and Valley Children's Hospital, Fresno, California. Consent for participation was obtained from the parent (see Appendix F) and assent from the child (see Appendix G), when age-appropriate. The study procedure described below is diagrammed in Appendix H.

The child was instructed in the use of the Oucher (Beyer, 1984). In order to evaluate the appropriateness of the photographic or numerical scale for self-report of the child's pain intensity, the child was asked to count from 0 to 100, and to identify which of 2 numbers presented by the investigator is larger. Children who were unable to perform both of these tests accurately were

instructed in the use of the photographic scale.

Demographic data obtained from the chart review and parental completion of a questionnaire included: age, weight, sex, number of siblings, birth order, most recent episode of tonsillitis, medication allergies, highest grade completed by each of the child's parents, ethnicity of each of the parents, household income, family history of pain problems, parental assessment of the child's ability to cope with pain following surgery, child's previous hospitalizations and/or surgery, child's most painful experience, ASA level, type of surgical procedure, indication for surgery, surgeon, anesthesiologist, preoperative hemoglobin (Hgb), hematocrit (Hct), platelet count, prothrombin time (PT), partial thromboplastin time (PTT), type of anesthetic, intraoperative drugs (other than the study drug), total anesthesia time, total surgery time, estimated blood loss, surgical technique, and hemostatic technique.

After completing the baseline measures and the preoperative instruction, children were randomized to either the experimental or the control group. To accrue approximately an equal number of children in each group, a specific blind randomization procedure was used. One of the faculty used a computer program to provide random number assignment. The group assignment (i.e., experimental or control) was placed in a sealed manilla envelope. The investigator, who was blind to the intervention, attached the sealed envelope to the patient's chart.

Anesthesia was maintained by nitrous oxide with halothane or isoflurane

and oxygen. No analgesics or local anesthetics other than the study drug were administered, although some patients did receive prophylactic anti-emetics (i.e., metoclopramide, hydroxyzine, or droperidol) or midazolam as part of their anesthetic regimen. Subjects receiving these drugs were equally distributed among the treatment groups. To protect the single-blind design of the study, the group assignment was sealed in a manilla envelope and accompanied the patient to surgery. The anesthesiologist opened the envelope and administered either an IM injection of normal saline (1 cc) or ketorolac (1 mg/kg) into the deltoid muscle at the completion of surgery before returning the patient to the post-anesthesia care unit (PACU). The identity of the study drug was not revealed to the PACU nurses, the parents, the child, or to the investigator who made the clinical assessments.

Evaluation of Pain Intensity and Severity and Duration of Bleeding

In the PACU, pain was assessed by both a self-report measure, using the Oucher (0 = no hurt, to 5 = the worst hurt you can imagine), and a behavioral measure, using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS; scored from 5 = no hurt to 13 = the worst hurt). Supplemental doses of fentanyl (0.5 mcg/kg/dose) were administered based on the PACU nurse's assessment of the child's level of pain. Pain intensity measures were obtained using the Oucher and the CHEOPS pre-fentanyl administration and 5 minutes after, for each dose of drug administered. The 5 minute time interval was selected based on pharmacokinetic data that demonstrate that maximal

analgesic effect is achieved within 5 minutes following the IV administration of fentanyl (Schachtel, 1992).

If no supplemental analgesics were required, then pain intensity measures were obtained at 30 minute intervals until discharge from the PACU. In the ambulatory surgery room, both pain intensity measures were obtained hourly until discharge. The duration of bleeding was evaluated by measuring the length of time (in minutes) from the time of admission to the PACU to the time that the postoperative bleeding was completely resolved. The severity of postoperative bleeding was measured using a 4-point rating scale at the following intervals: upon arrival in the PACU, at each fentanyl administration time, upon discharge from PACU, and then hourly until discharge home.

Data Analysis

Descriptive statistics were done to summarize sample characteristics. The treatment groups demographic characteristics were compared using a Student's t-test or Chi-square analysis. Individual study aims were evaluated using a one-way ANOVA, a two-way repeated measures ANOVA, a Student's t-test, or Chi-square analysis. All calculations used actual values. Adjustments were not made for missing data; therefore, the cohort for analysis was dependent upon the largest complete set of data across groups. A p-value of <0.05 was considered statistically significant.

Chapter 4

RESULTS

A randomized clinical trial was conducted to compare the analgesic requirements, pain intensity scores, severity and duration of bleeding, and length of stay, between children who received either an IM injection of ketorolac (1 mg/kg) or an IM injection of saline (1 ml) at the completion of a tonsillectomy with or without adenoidectomy. The sample consisted of 87 children (45 in the experimental group and 42 in the control group). The refusal rate was 5.4%. One child in the control group experienced significant postoperative edema, requiring supplemental oxygen to maintain adequate saturation. This patient was held in the PACU for an extended time, and then transferred to the acute care unit for overnight observation. The child who was admitted was excluded from the data analysis.

Demographic Data

A. Saline Group (N=42)

1. **Patient Characteristics** - The majority of the children (52.4%) in the saline group (N=42) were male with a mean age of 85.00 months (approximately 7 years of age; S.D.=26.78 months, range 45 to 140 months). The mean weight of the children was 30.66 kilograms (S.D.=12.47 kgs). Approximately 34% of the children in the saline group had an episode of tonsillitis within the past month, while 36.6% of the children had not had an episode of tonsillitis prior to the surgical procedure. Most of the children had

not been hospitalized previously (88.1%) or had not had a previous history of surgery (73.8%). The patient characteristics for the saline group are summarized in Table 3.

2. **Parental Characteristics** - The largest percentage of fathers in the sample were Caucasian (48.8%) with Hispanics being the second largest (29.3%) ethnic group represented. The same pattern was seen with the mothers with 57.1% being Caucasian and 26.2% being Hispanic. The mean number of years of education for the fathers and mothers was 12.68 (S.D.=2.17) and 12.50 (S.D.=2.95), respectively. The majority of the families (67%) had an average yearly household income of between $10,000 and $40,000. A summary of the parental characteristics is presented in Table 4.

3. **Surgical Characteristics** - The American Society of Anesthesiologist's (ASA) Physical Status Classification demonstrated that 81% of the children were ASA level I (i.e., a normal, healthy patient) and 19% were ASA level II (i.e., a patient with mild systemic disease).

The indications for surgery in the saline group were recurrent tonsillitis (35.7%), a history of apnea and obstructive airway disease (28.6%), or a history of recurrent tonsillitis with apnea and obstructive airway disease (35.7%). The majority of the children (59.5%) underwent a tonsillectomy with an adenoidectomy.

The mean anesthesia time was 40.57 minutes (S.D.=13.57) and the mean surgery time was 25.02 minutes (S.D.=9.86). The mean estimated blood loss

intraoperatively was 23.55 milliliters (S.D.=19.05). The surgical characteristics of the saline group are summarized in Table 5.

B. Ketorolac Group (N=45)

1. **Patient Characteristics** - The majority of the children (57.8%) in the ketorolac group (N=45) were male with a mean age of 84.67 months (approximately 7 years of age; S.D.=28.91, range 46 to 150 months). The mean weight of the children was 36.67 kilograms (S.D.=11.99). Approximately 47% of children in the ketorolac group had an episode of tonsillitis within the past month, while 24.4% of the children had not had an episode of tonsillitis prior to the surgical procedure. The majority of the children had never been hospitalized before (86.7%) or undergone a previous surgical procedure (84.4%). The patient characteristics for the ketorolac group are summarized in Table 3.

2. **Parental Characteristics** - The majority of the fathers in the sample were Caucasian (48.9%), with Hispanics being the second largest (35.6%) ethnic group represented. Similar findings were observed with the mothers, with 57.8% being Caucasian and 35.6% being Hispanic. The mean number of years of education for the fathers and mothers were 12.47 (S.D.=2.63) and 12.11 (S.D.=2.58), respectively. The majority of the families (56.9%) had an average yearly household income of between $10,000 and $40,000. A summary of the parental characteristics is presented in Table 4.

3. **Surgical Characteristics** - The majority of the children in the ketorolac

group (82.2%) were ASA level I and 17.8% were ASA level II. The indications for surgery were recurrent tonsillitis (42.2%); a history of apnea and obstructive airway disease (40.0%); or a history of both tonsillitis and apnea/obstructive airway disease (17.8%). The majority of the children (57.8%) underwent a tonsillectomy with an adenoidectomy.

The mean anesthesia time was 36.07 minutes (S.D.=10.89) and the mean surgery time was 24.64 minutes (S.D.=9.45). The mean estimated intraoperative blood loss was 19.93 milliliters (S.D.=13.85). The surgical characteristics of the ketorolac group are summarized in Table 5.

C. Comparison of the Saline and Ketorolac Groups

The saline and ketorolac groups were comparable in terms of all patient, parental, and surgical characteristics. No statistically significant differences were demonstrated for any of the variables listed in Tables 3 through 5 using either independent Student's t-tests or Chi-Square analyses.

Table 3

Patient Characteristics

	Saline Group Mean (S.D.) (N=42)	Ketorolac Group Mean (S.D.) (N=45)	Statistical Analyses
Age (months)	85.00 (26.73)	84.67 (28.91)	t=-0.056, p=0.956
Weight (kg)	30.66 (12.47)	36.67 (11.99)	t=-1.520, p=0.132
	% (N)	% (N)	
Gender			
Male	52.4% (22)	57.8% (26)	χ^2=.084
Female	47.6% (20)	42.2% (19)	p=0.613
Last Infection			
< 2 weeks	14.6% (6)	22.2% (10)	
3-4 weeks	19.5% (8)	24.4% (11)	χ^2=1.067
> 1 month	29.3% (12)	28.9% (13)	p=0.785
Not applicable	36.6% (15)	24.4% (11)	
Previous Hospitalization			
Yes	11.9% (5)	13.3% (6)	χ^2=0.000
No	88.1% (37)	86.7% (39)	p=1.000
Previous Surgery			
Yes	26.2% (11)	15.6% (7)	χ^2=0.919
No	73.8% (31)	84.4% (38)	p=0.338

Table 4

Parental/Family Characteristics

	Saline Group (N=42)	Ketorolac Group (N=45)	Statistical Analyses
	% (N)	% (N)	
Father's Ethnicity			
Caucasian	48.8% (20)	48.9% (22)	
Hispanic	29.3% (12)	35.6% (16)	
African American	9.8% (4)	8.9% (4)	χ^2=0.12
Asian	2.4% (1)	0.0% (0)	p=0.99
American Indian	2.4% (1)	2.2% (1)	
Other	7.2% (3)	4.4% (2)	
Mother's Ethnicity			
Caucasian	57.1% (24)	57.8% (26)	
Hispanic	26.2% (11)	35.6% (16)	
African American	4.8% (2)	4.4% (2)	χ^2=0.93
Asian	2.4% (1)	0.0% (0)	p=0.97
American Indian	4.8% (2)	0.0% (0)	
Other	4.8% (2)	2.2% (1)	
Household Income			
$10,000 or less	19.0% (8)	26.7% (12)	
$10,001-$20,000	16.7% (7)	26.7% (12)	
$20,000-$30,000	21.4% (9)	17.8% (8)	χ^2=1.16
$30,001-$40,000	16.7% (7)	11.1% (5)	p=0.89
Greater than $40,000	21.4% (9)	15.6% (7)	
No response	5.0% (2)	2.2% (1)	
	Mean (S.D.)	Mean (S.D.)	
Father's Years of Education	12.68 (2.17)	12.47 (2.63)	t=-0.41 p=0.69
Mother's Years of Education	12.50 (2.95)	12.11 (2.58)	t=-0.66 p=0.51

Table 5

Surgical Characteristics

	Saline Group (N=42)	Ketorolac Group (n=45)	Statistical Analyses
	% (N)	% (N)	
ASA Level			
I	81.0% (34)	82.2% (37)	χ^2=0.00
II	19.0% (8)	17.8% (8)	p=1.00
Indication for Surgery			
Tonsillitis	35.7% (15)	42.2% (19)	
Apnea/Obstructive Airway	28.6% (12)	40.0% (18)	χ^2=3.33 p=0.65
Tonsillitis/ Apnea/Obstructive Airway	35.7% (15)	17.8% (8)	
Type of Surgery			
T	9.5% (4)	13.3% (6)	
T + A	59.5% (25)	57.8% (26)	χ^2=1.16
T + A + M	31.0% (13)	28.9% (13)	p=1.00
	Mean (S.D.)	Mean (S.D.)	
Total Anesthesia Time (minutes)	40.57 (13.57)	36.07 (10.89)	t=-1.71 p=0.09
Total Surgery Time (minutes)	25.02 (9.86)	24.64 (9.45)	t=-1.63 p=0.11
Discharge Time from PACU	72.56 (23.91)	68.42 (18.94)	t=-0.88 p=0.38
Estimated Blood Loss Intraoperatively (cc's)	23.55 (19.05)	19.93 (13.85)	t=-1.01 p=0.32

T, Tonsillectomy; A, Adenoidectomy; M, Myringotomy

Specific Aims

A. Specific Aim #1 - To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on the amount of fentanyl administered postoperatively.

Independent, Student t-tests were done to determine if there were statistically significant differences between the saline group and the ketorolac group, in the total microgram dose of fentanyl administered in the PACU, in the day surgery area, and for the entire postoperative period. The data are summarized in Table 6.

No statistically significant differences in total fentanyl dose administered in the PACU were observed between the saline group ($\bar{X}=38.16\pm3.88$) and the ketorolac group ($\bar{X}=32.88\pm2.58$; Figure 2A). In the day surgery area, the ketorolac group received statistically significantly less fentanyl ($\bar{X}=13.83\pm1.62$) than the saline group ($\bar{X}=22.72\pm3.48$, $t=-2.32$, $p<0.03$; Figure 2B). The children in the ketorolac group received statistically significantly less fentanyl overall ($\bar{X}=35.91\pm2.50$) than the children in the fentanyl group ($\bar{X}=48.32\pm5.04$; $t=-2.21$, $p<0.03$; Figure 3).

Table 6

Postoperative Fentanyl Requirements

	Saline Group (N=42)	Ketorolac Group (N=45)	Significance Level
	Mean (S.E.) (N)	Mean (S.E.) (N)	
Total fentanyl dose (mcg) administered in PACU	38.16 (3.88) (N=40)	32.88 (2.57) (N=43)	t=-1.13 p=0.26
Total fentanyl dose (mcg) administered in Day Surgery	22.72 (3.48) (N=20)	13.83 (1.62) (N=12)	t=-2.32 p=0.03
Total fentanyl dose (mcg) for the entire postoperative period	48.32 (5.04) (N=41)	35.91 (6.63) (N=44)	t=-2.21 p=0.03

Figure 2A - The total fentanyl dose administered in the PACU in children who received intramuscular saline (N=40) or intramuscular ketorolac (1 mg/kg; N=43) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy.

Figure 2B - The total fentanyl dose administered in the Day Surgery area in children who received intramuscular saline (N=20) or intramuscular ketorolac (1 mg/kg; N=12) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy.

Dose is reported in micrograms. Each bar in the figure represents the mean $\pm$ S.E.M. The asterisk above the bar denotes a statistically significant difference.

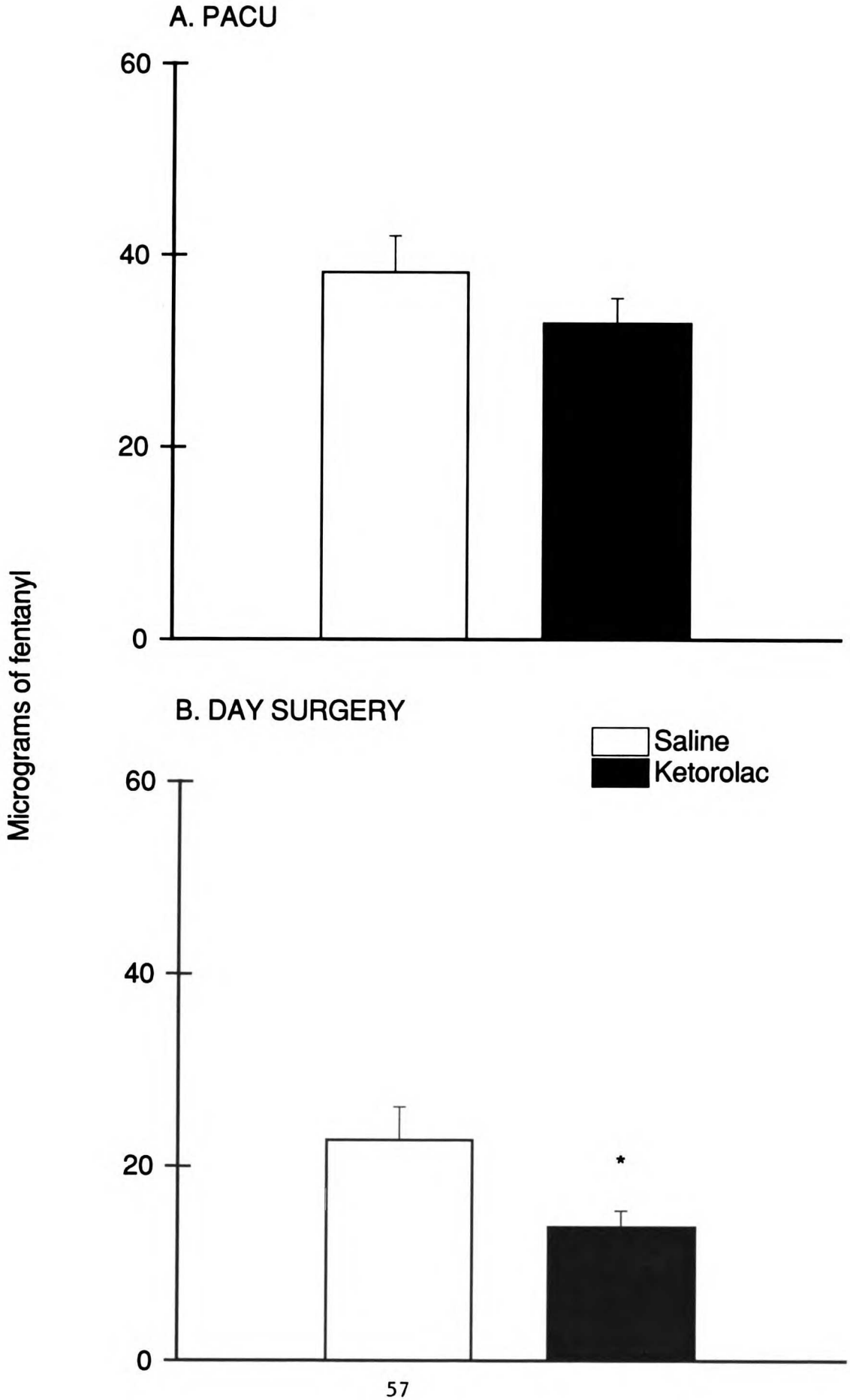
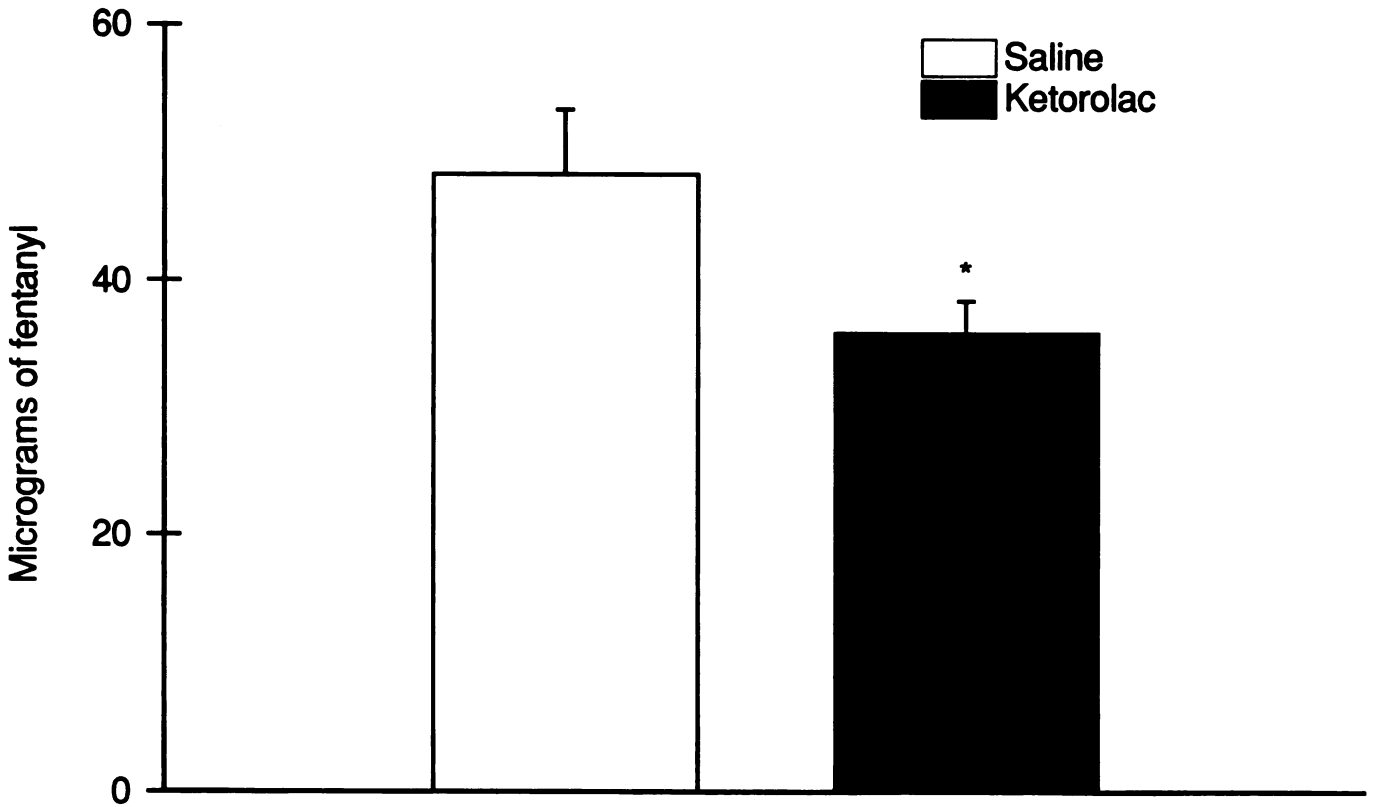


Figure 3 - The total fentanyl dose administered during the entire ambulatory surgery stay, in children who received intramuscular saline (N=41) or intramuscular ketorolac (1 mg/kg; N=44) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. Dose is reported in micrograms. Each bar in the figure represents the mean $\pm$ S.E.M. The asterisk above the bar denotes a statistically significant difference.



B. Specific Aim #2 - To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on children's postoperative pain intensity scores.

To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on children's postoperative pain intensity scores, changes in the pre-drug pain intensity scores of both the CHEOPS and the photographic scale of the Oucher were evaluated over repeated fentanyl administrations in the PACU, and at hourly intervals in the Day Surgery area.

1. CHEOPS Scores in the PACU

The CHEOPS pain intensity scores for the saline and ketorolac groups, prior to each drug administration in the PACU, are illustrated in Figure 4A. One-way analysis of variance (ANOVA) for the first 3 administration times demonstrated a statistically significant decrease in pre-drug CHEOPS scores in the ketorolac group ($F(2,30)=5.34$, $p<0.01$), but not in the saline group ($F(2,24)=2.46$, $p>0.05$).

A two-way, repeated measures ANOVA for the first 3 administration times demonstrated a statistically significant main effect of time ($F(2.54)=6.98$, $p<0.002$), but not of group ($F(1.27)=3.70$, $p=0.065$). These data suggest that the administration of ketorolac at the end of surgery is effective in reducing pain intensity scores, over time, in the PACU.

2. Oucher Scores in the PACU

Figure 4B illustrates the photographic Oucher scores prior to each fentanyl

administration in the PACU. One-way ANOVA could not be performed for either the saline or the ketorolac groups because of the unequal and sometimes exceedingly small numbers of children at each drug administration time. No conclusions about the efficacy of ketorolac can be drawn from the data obtained using the Oucher in the PACU.

It should be noted that, only 4% of the children receiving fentanyl (3/83) in the study could complete a pain intensity rating using the Oucher at the first drug administration time ($\bar{X}$=14.30 minutes after arrival in the PACU, S.D.=7.83). At the second drug administration time ($\bar{X}$=30.66 minutes, S.D.=13.81), 42% of the children receiving fentanyl (25/59) completed a pain intensity rating. By the third administration time ($\bar{X}$=51.17 minutes, S.D.=18.80), 70% of the children receiving fentanyl (20/29) were able to rate their pain intensity using the Oucher. At the fourth administration time ($\bar{X}$=67.14 minutes, S.D.=28.84), 43% of the children receiving fentanyl (3/7) completed a rating using the Oucher.

3. Hourly CHEOPS Scores in Day Surgery

The hourly CHEOPS pain intensity scores, in Day Surgery, for the saline and ketorolac groups are illustrated in Figure 5A. No significant differences were demonstrated in pain intensity scores over time for either the saline group ($F(4,104)=0.85$, $p=0.50$) or the ketorolac group ($F(4,84)=0.55$, $p=0.70$), using one-way ANOVA.

4. Hourly Oucher Scores Using the Photographic Scale in Day Surgery

The hourly pain intensity scores, using the photographic scale of the Oucher, are illustrated in Figure 5B. One-way ANOVA demonstrated a statistically significant decrease in hourly Oucher pain intensity scores in both the saline group ($F(4,76)=5.14$, $p=0.001$) and in the ketorolac group ($F(4,68)=3.64$, $p<0.001$).

Figure 4A - Mean pre-drug CHEOPS pain intensity scores in the PACU, in children who received intramuscular saline or intramuscular ketorolac (1 mg/kg) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent drug administration times (DAT; DAT #1 - $\bar{X}$=14.30 minutes after arrival in the PACU, S.D.=7.83; saline, N=40; ketorolac, N=43, DAT #2 - $\bar{X}$=30.66 minutes, S.D.=13.81; saline, N=26; ketorolac, N=33, DAT #3 - X=51.17 minutes, S.D.=18.80; saline, N=13; ketorolac, N=16, and DAT #4 - $\bar{X}$=67.14 minutes, S.D.=28.84; saline, N=4; ketorolac, N=3), when intravenous fentanyl was administered.

Figure 4B - Mean pre-drug Oucher pain intensity scores in the PACU, in children who received intramuscular saline or intramuscular ketorolac (1 mg/kg) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent drug administration times (DAT; DAT#1 - ($\bar{X}$=14.30 minutes after arrival in the PACU, S.D.=7.83; saline, N=1; ketorolac, N=2, DAT #2 - $\bar{X}$=30.66 minutes, S.D.=13.81; saline, N=10; ketorolac, N=15, DAT #3 - $\bar{X}$=51.17 minutes, S.D.=18.80; saline, N=9; ketorolac, N=11, and DAT #4 - $\bar{X}$=67.14 minutes, S.D.=28.84; saline, N=1; ketorolac, N=2), when intravenous fentanyl was administered.

Pre-drug pain intensity measures were taken immediately prior to administration of fentanyl. Post-drug measures were obtained 5 minutes after

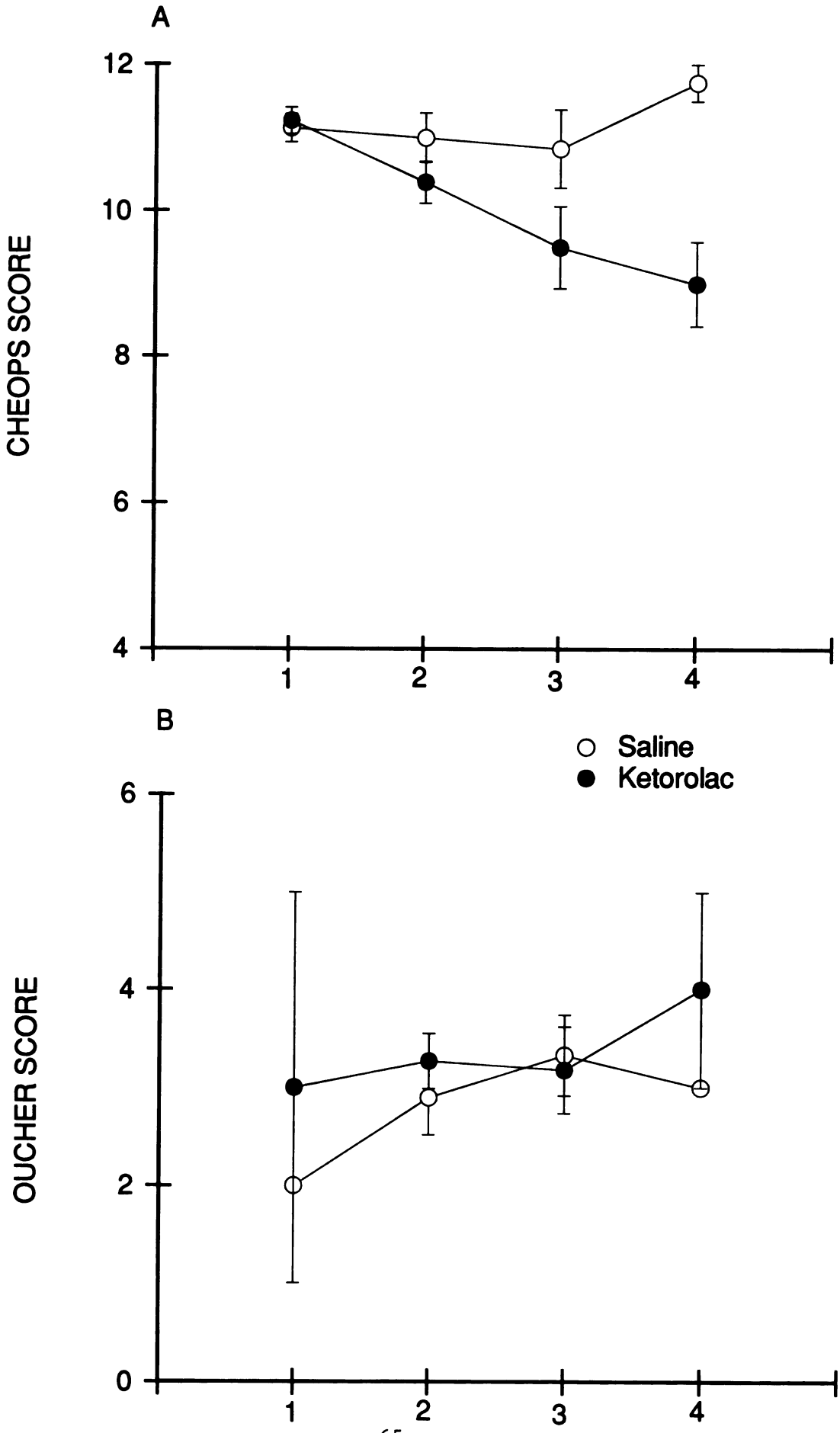
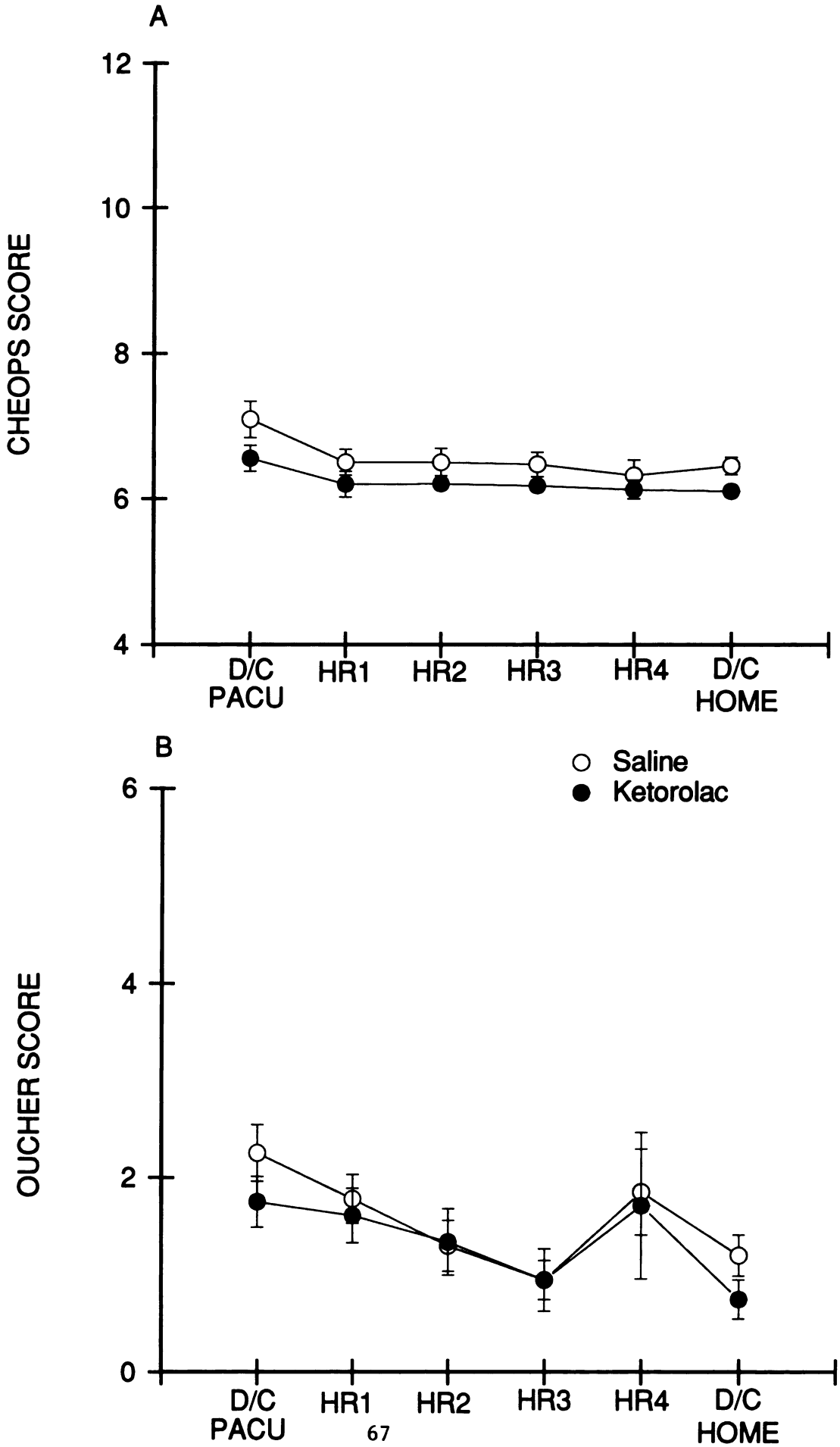


Figure 5A - The mean CHEOPS pain intensity scores in the Day Surgery area, in children who received intramuscular saline or intramuscular ketorolac (1 mg/kg) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent pain intensity scores at the time of discharge from the PACU (saline, N=41; ketorolac, N=45), at hour 1 in Day Surgery (saline, N=41; ketorolac, N=45), hour 2 in Day Surgery (saline, N=37; ketorolac, N=38), hour 3 in Day Surgery (saline, N=27; ketorolac, N=22), hour 4 in Day Surgery (saline, N=15; ketorolac, N=8), and at the time of discharge home (saline, N=41; ketorolac, N=45).

Figure 5B - The mean Oucher pain intensity scores in the Day Surgery area, in children who received intramuscular saline or intramuscular ketorolac (1 mg/kg) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent pain intensity scores at the time of discharge from the PACU (saline, N=32; ketorolac, N=35), at hour 1 in Day Surgery (saline, N=32; ketorolac, N=38), hour 2 in Day Surgery (saline, N=30; ketorolac, N=29), hour 3 in Day Surgery (saline, N=22; ketorolac, N=22), hour 4 in Day Surgery (saline, N=1; ketorolac, N=7), and at the time of discharge home (saline, N=35; ketorolac, N=40).

Each point in the figure represents the mean $\pm$ S.E.M. Some error bars are contained within the symbols.


A
12
10
8
6
4
CHEOPS SCORE
D/C PACU
HR1
HR2
HR3
HR4
D/C HOME
B
Saline
Ketorolac
6
4
2
0
OUCHER SCORE
D/C PACU
HR1
HR2
HR3
HR4
D/C HOME

C. Specific Aim #3 - To determine the effect of intermittent intravenous (IV) postoperative administration of fentanyl on pain intensity scores in the PACU, for children in the saline group and for children in the ketorolac group.

For the purposes of this analysis only the CHEOPS pain intensity scores were utilized, because of unequal and sometimes exceedingly small number of Oucher scores. The data are reported in Table 7.

1. Saline Group

CHEOPS pain intensity scores were measured immediately prior to each administration of fentanyl and 5 minutes after the administration of the drug. Figure 6A illustrates the effect of fentanyl, at each drug administration, on CHEOPS scores in the saline group. Independent Student t-tests, done at each administration time, determined that there was a statistically significant decrease in CHEOPS pain intensity scores at drug administration time (DAT) #1 ($t=10.27$, $p<0.00001$), DAT #2 ($t=9.03$, $p<0.00001$), and DAT #3 ($t=3.63$, $p<0.004$), but not at DAT #4 ($t=2.65$, $p<0.08$).

2. Ketorolac Group

Figure 6B illustrates the effect of fentanyl, at each drug administration, on CHEOPS scores in the ketorolac group. Independent Student t-tests, done at each drug administration time, determined that there was a statistically significant decrease in CHEOPS pain intensity scores at DAT #1 ($t=10.94$, $p<0.00001$), DAT #2 ($t=6.49$, $p<0.00001$), and DAT #3 ($t=4.38$, $p<0.0005$), but

Table 7

CHEOPS Pain Intensity Scores in the PACU
Pre- and Post-Fentanyl Administration

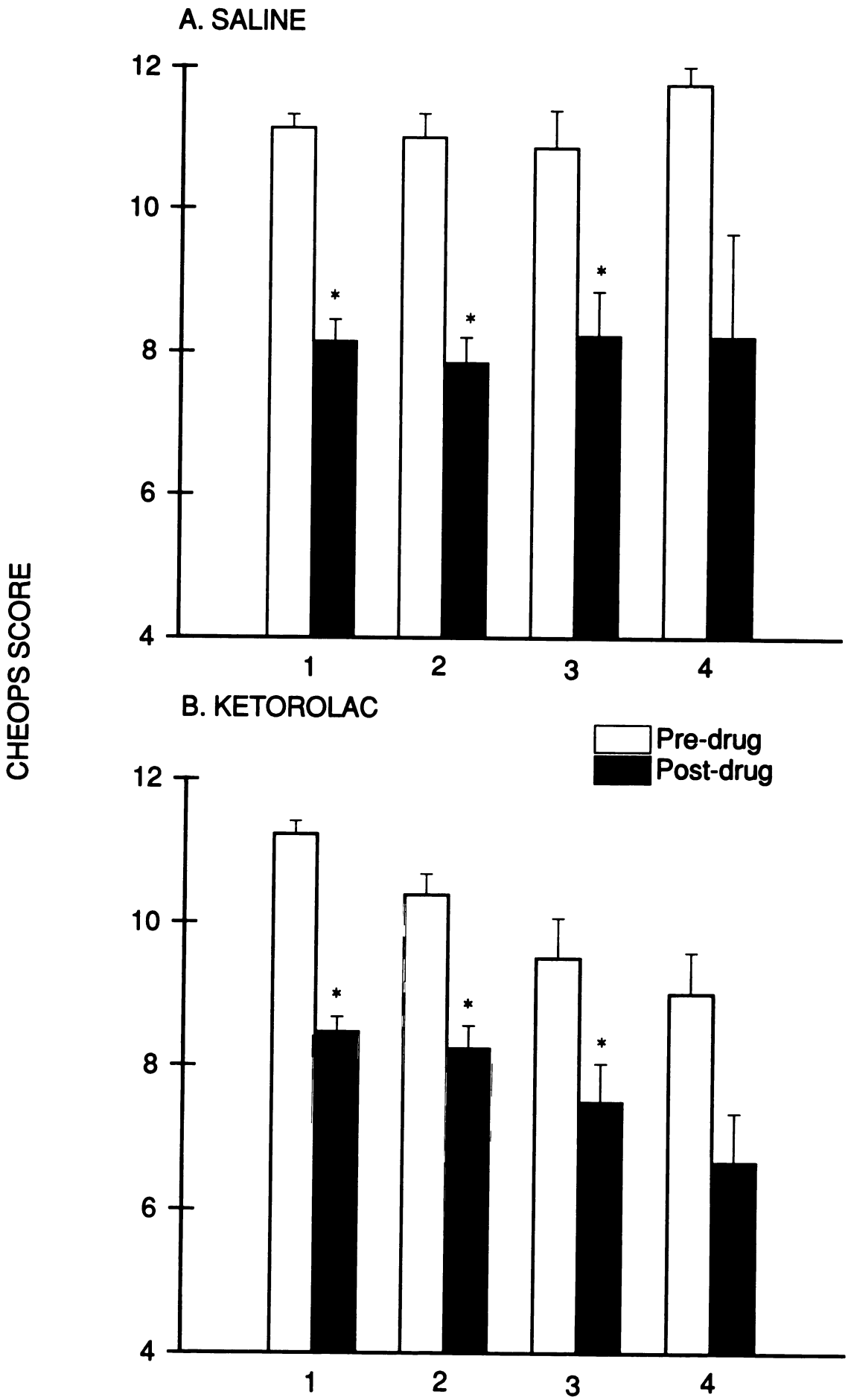
	DAT #1	DAT #2	DAT #3	DAT #4
	Mean (S.E.) (N)	Mean (S.E.) (N)	Mean (S.E.) (N)	Mean (S.E.) (N)
Pre-Fentanyl				
Saline Group	11.13 (0.19) (N=40)	11.00 (0.34) (N=26)	10.85 (0.53) (N=13)	11.75 (0.25) (N=4)
Ketorolac Group	11.23 (0.18) (N=43)	10.39 (0.29) (N=33)	9.50 (0.56) (N=16)	9.00 (0.58) (N=3)
Post-Fentanyl				
Saline Group	8.15 (0.30) (N=40)	7.85 (0.35) (N=26)	8.23 (0.61) (N=13)	8.25 (1.44) (N=4)
Ketorolac Group	8.47 (0.20) (N=43)	8.24 (0.31) (N=33)	7.50 (0.53) (N=16)	6.67 (0.67) (N=3)

DAT = Drug Administration Time

Figure 6A - The effects of intravenous bolus fentanyl administration in the PACU, on CHEOPS pain intensity scores, in children who received intramuscular saline at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent drug administration time one (DAT #1; $\bar{X}$=14.30 minutes after arrival in the PACU, S.D.=7.83; N=40), DAT #2 ($\bar{X}$=30.66 minutes, S.D.=13.81; N=26), DAT #3 ($\bar{X}$=51.17 minutes, S.D.=18.80; N=13), and DAT #4 ($\bar{X}$=67.14 minutes, S.D.=28.84; N=4), in which intravenous fentanyl was administered.

Figure 6B - The effects of intravenous bolus fentanyl administration in the PACU, on CHEOPS pain intensity scores in children who received intramuscular ketorolac (1 mg/kg) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy. The integers below the scores on the x-axis represent DAT #1 ($\bar{X}$=14.30 minutes after arrival in the PACU, S.D.=7.83; N=43), DAT #2 ($\bar{X}$=30.66 minutes, S.D.=13.81; N=33), DAT #3 ($\bar{X}$=51.17 minutes, S.D.=18.80; N=16), and DAT #4 ($\bar{X}$=67.14 minutes, S.D.=28.84; N=3), in which intravenous fentanyl was administered.

Pre-drug pain intensity measures were obtained immediately prior to fentanyl administration, and post-drug pain intensity measures were obtained 5 minutes after the administration of fentanyl. Each bar in the figure represents the mean $\pm$ S.E.M. Some error bars are contained with the bar graph.


A. SALINE
12
10
8
6
4
CHEOPS SCORE
*
*
*
1
2
3
4
B. KETOROLAC
Pre-drug
Post-drug
12
10
8
6
4
*
*
*
1
2
3
4

D. Specific Aim #4 - To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on the severity and duration of postoperative bleeding.

The severity of postoperative bleeding in both the saline and ketorolac groups was evaluated at the time of admission to the PACU, at the time of discharge from the PACU, at hourly intervals in the Day Surgery area, and at the time of discharge from the hospital, using a 4-point rating scale. The results are summarized in Table 8.

1. Saline Group

Mild bleeding was observed in 45.27% of the children (N=19) in the saline group (N=42) upon arrival in the PACU. In all of the children in the saline group, bleeding had ceased by the time of discharge from the PACU.

2. Ketorolac Group

Mild bleeding was demonstrated by 44.4% of the children (N=20) in the ketorolac group (N=45) upon arrival in the PACU. Postoperative bleeding was resolved prior to discharge from the PACU in the all but one child, who experienced mild bleeding which persisted 3 hours beyond discharge from the PACU. Bleeding in this child resolved spontaneously prior to discharge.

Table 8

Severity of Postoperative Bleeding

	Saline Group (N=42)	Ketorolac Group (N=45)	Statistical Analyses
	% (N)	% (N)	
PACU Arrival			
No Bleeding	54.76% (N=23)	55.56% (N=25)	χ=0.00
Mild Bleeding	45.24% (N=19)	44.40% (N=20)	p=1.00
Discharge from PACU			
No Bleeding	100.00% (N=41)	97.78% (N=44)	χ=0.00
Mild Bleeding	0.00% (N=0)	2.22% (N=1)	p=1.00
Hour 1 Day Surgery			
No Bleeding	100.00% (N=41)	97.78% (N=44)	χ=0.00
Mild Bleeding	0.00% (n=0)	2.22% (N=1)	p=1.00
Hour 2 Day Surgery			
No Bleeding	100.00% (N=41)	97.37% (N=37)	χ=0.00
Mild Bleeding	0.00% (N=0)	2.63% (N=1)	p=1.00
Hour 3 Day Surgery			
No Bleeding	100.00% (N=27)	95.45% (N=21)	χ=0.01
Mild Bleeding	0.00% (N=0)	4.55% (N=1)	p=0.92
Discharge Home			
No Bleeding	100.00% (N=41)	100.00% (N=45)	
Mild Bleeding	0.00% (N=0)	0.00% (N=0)	

E. <u>Specific Aim #5</u> - To determine the effect of a single IM dose of ketorolac, administered at the completion of surgery, on the length of stay in ambulatory surgery.

Independent Student t-tests were done to determine if there were statistically significant differences between the saline group and the ketorolac group, in the length of stay in the PACU, in the Day Surgery area, and for the entire postoperative period.

No statistically significant differences in the number of minutes in PACU was observed between the saline group ($\bar{X}=72.56\pm3.74$) and the ketorolac group ($\bar{X}=68.42\pm2.82$; Figure 7A). In the Day Surgery area, children in the ketorolac group ($\bar{X}=193.87\pm9.87$) were discharged 25 minutes sooner than children in the saline group ($\bar{X}=218.85\pm9.50$; Figure 7B), although the difference was not statistically significant (t=-1.817, p=0.07).

The average length of stay, in minutes, for children in the saline group ($\bar{X}=291.42$, S.D.=53.24) was compared to children in the ketorolac group ($\bar{X}=262.29$, S.D.=66.47), using a Student's t-test. The children in the ketorolac group were discharged approximately 30 minutes sooner than the children in the saline group (t=-2.23, p=0.029; Figure 8).

Figure 7A - The mean length of stay in the PACU for children who received intramuscular saline (N=42) or intramuscular ketorolac (1 mg/kg; N=45) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy.

Figure 7B - The mean length of stay in the Day Surgery area for children who received intramuscular saline (N=42) or intramuscular ketorolac group (1 mg/kg; N=45) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy.

Time is reported in minutes. Each bar in the figure represents the mean $\pm$ S.E.M. The asterisk above the bar denotes statistical significance.

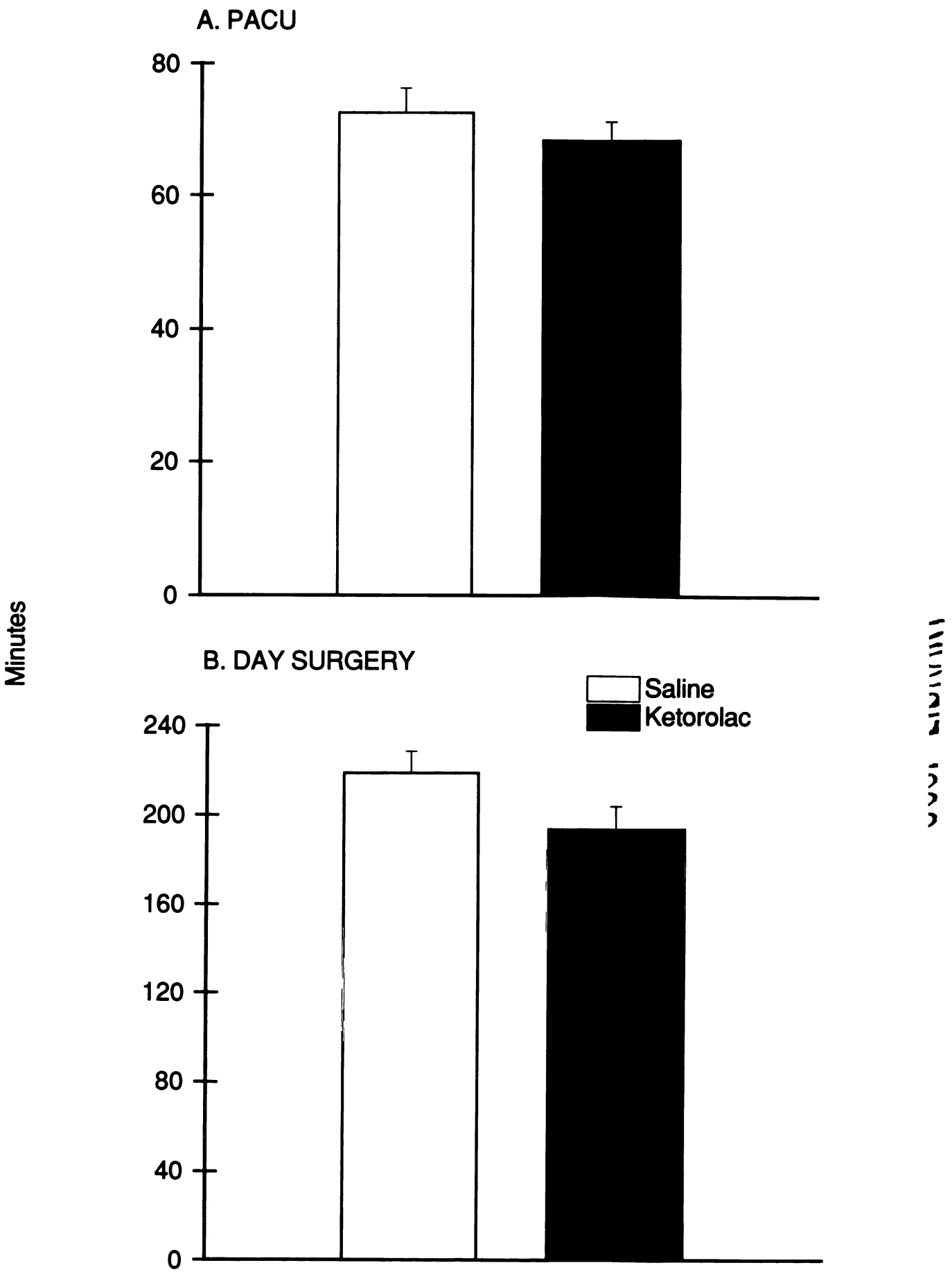
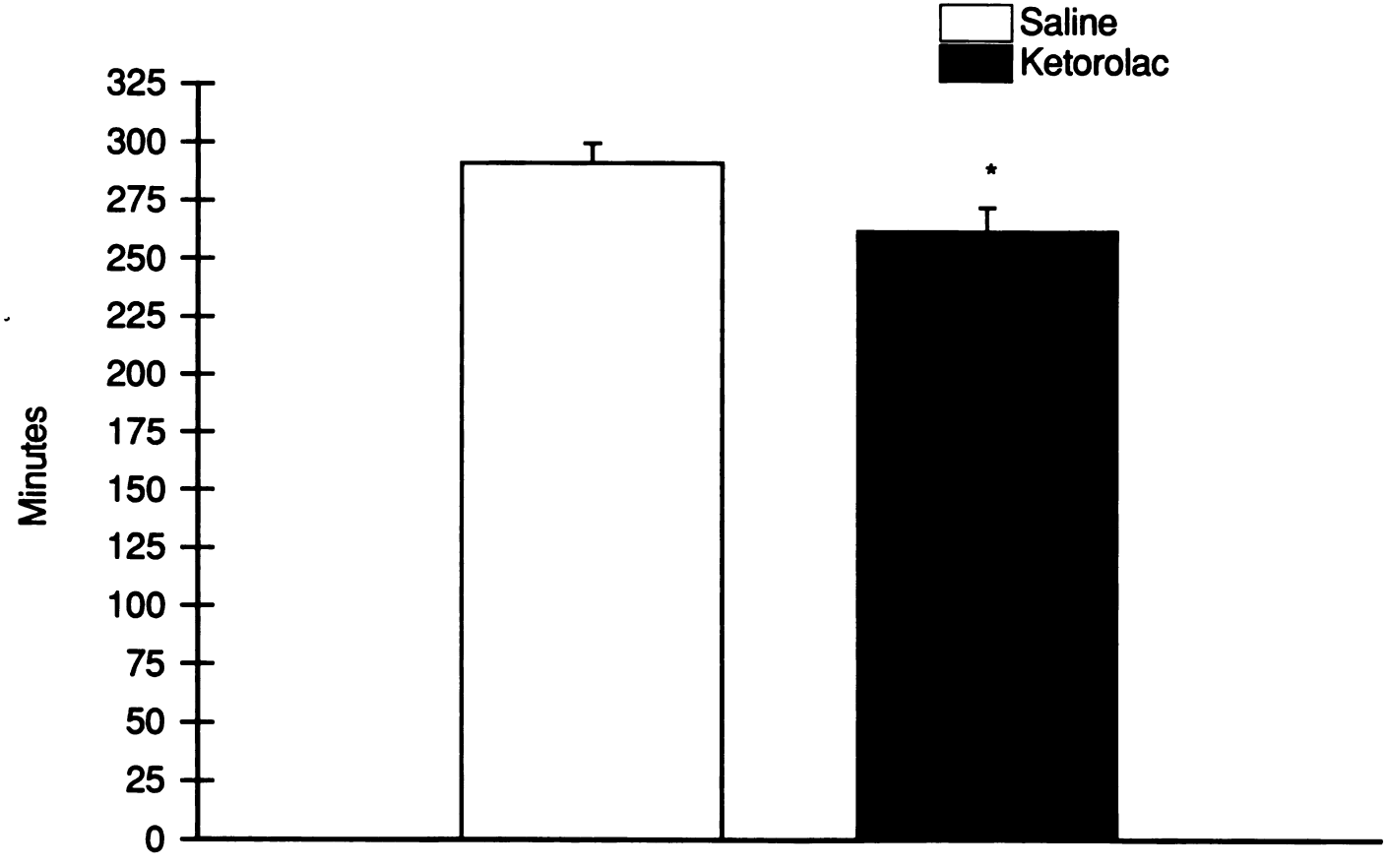

A. PACU
80
60
40
20
0
Minutes
B. DAY SURGERY
Saline
Ketorolac
240
200
160
120
80
40
0

Figure 8 - The total length of stay in ambulatory surgery for children who received intramuscular saline (N=42) or intramuscular ketorolac (1 mg/kg; N=45) at the completion of surgery, for the treatment of postoperative pain following tonsillectomy.

Time is reported in minutes. Each bar in the figure represents the mean ± S.E.M. The asterisk above the bar denotes statistical significance.


Saline
Ketorolac
Minutes
325
300
275
250
225
200
175
150
125
100
75
50
25
0
*

Chapter 5

DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

A randomized clinical trial was conducted in children undergoing tonsillectomy, with or without adenoidectomy, to compare the analgesic requirements, postoperative pain intensity scores, severity and duration of postoperative bleeding, and length of ambulatory surgery stay between children who received a single IM dose of normal saline at the completion of surgery with children who received a single IM dose of ketorolac at the completion of surgery.

Discussion

The results of this study in children undergoing tonsillectomy, with or without adenoidectomy, demonstrate that a single IM dose of ketorolac, given at the completion of surgery, significantly reduces the total amount of fentanyl administered during the entire postoperative period in an ambulatory surgery setting. The difference in total dose administered was largest in the Day Surgery area as compared to the PACU. While there were no significant differences in the amount of fentanyl administered to either group in the PACU, children in the ketorolac group received 39% less fentanyl than children in the saline group ($p<0.05$).

The absence of a difference in the total dose of fentanyl administered in the PACU may be due to the timing of administration of the ketorolac (i.e., at the completion of surgery). The mean discharge time from PACU for both groups

was 70.40 minutes (S.D.=21.42). Peak analgesia following IM administration of ketorolac, is reported to occur within 75 to 150 minutes (Dipalma, 1991; Estenne et al., 1988; O'Hara et al., 1987; Yee et al., 1986), which coincides with the beginning of the children's stay in the Day Surgery area. The marked reduction in fentanyl administered in the Day Surgery area, and the smaller number of children in the ketorolac group (N=12) compared to the saline group (N=20) who received supplemental doses of fentanyl, suggests that the analgesic effect occurs within approximately one hour following administration in children. In subsequent studies, the administration time of ketorolac could be varied (e.g., administration of the dose earlier in the procedure), to determine if the total dose of opioid administered in the PACU and throughout the entire postoperative period would be reduced.

This study is one of the only investigations to examine the efficacy of IV bolus administration of fentanyl as a postoperative analgesic in children undergoing ambulatory surgery. Fentanyl significantly reduced the amount of postoperative pain in both groups of children (Figures 6A and 6B). However, the analgesia was of brief duration, lasting approximately 15 minutes, and many children required a second (N=59) and third (N=29) bolus dose of fentanyl, approximately every 15 minutes for the first 45 minutes in the PACU, and at least one additional dose of fentanyl in Day Surgery (N=32). Additional studies, using different doses of fentanyl, are warranted in the postoperative period to determine if analgesic efficacy and duration of analgesia, can be enhanced

without an increase in side-effects.

As part of this study, the severity of pain associated with tonsillectomy was evaluated using a behavioral and a self-report measure in both the PACU and Day Surgery areas. The mean CHEOPS pain intensity scores in the PACU prior to IV fentanyl administration were relatively high ranging between 9 and 12 (maximum score on the CHEOPS is 13) for children in both the saline and ketorolac groups. These scores are higher than the pre-drug CHEOPS pain intensity scores observed with children (ages 1 to 7) undergoing circumcision (reported to range from 9 to 10 in the PACU; McGrath et al., 1985).

In the PACU, the pre-drug CHEOPS scores in the ketorolac group decreased over time, whereas the saline group pre-drug scores remained unchanged over the first hour. Following the administration of fentanyl, to both groups, post-drug CHEOPS scores decreased. Our data suggest that tonsillectomy produces relatively severe pain in children in the immediate postoperative period and that the CHEOPS was a useful tool to evaluate changes in pain intensity over time and in response to analgesics in the immediate postoperative period. Additional studies are needed, to determine the usefulness of the CHEOPS in discriminating the pain intensity associated with different surgical procedures.

Pain intensity measures were also obtained in the Day Surgery area. Of note, in the Day Surgery area, there were no differences in pain intensity scores, (evaluated using the Oucher), between the saline and the ketorolac

groups. However, the children in the saline group received more fentanyl than the children in the ketorolac group. These data suggest that the pain following tonsillectomy, with or without adenoidectomy, was well controlled in the Day Surgery area in both the saline and ketorolac groups, either because ketorolac enhanced the efficacy of fentanyl, or because children in the saline group received sufficient supplemental doses of fentanyl. The increase in pain intensity scores reported using the Oucher, at 4 hours in Day Surgery, for both groups (Figure 5B), may be due to mechanical irritation associated with increased fluid intake prior to discharge home.

A clinically significant finding from this study provides direction for the appropriate use of assessment tools in the postoperative period. In the immediate postoperative period (i.e., PACU; Figure 4A and 4B), the behavioral assessment tool (i.e., CHEOPS) was a more sensitive and reliable measure of pain intensity because children could not cooperate and provide ratings of pain intensity using the Oucher. In addition, following the administration of fentanyl, children were too sedated to accurately report pain intensity scores. In contrast, in the Day Surgery area (Figure 5A and 5B), the self-report measure (i.e., Oucher), was more sensitive to changes in pain intensity over time, compared to the behavioral measure (i.e., CHEOPS).

Similar discrepancies between self-report and behavioral measures were reported by Beyer and colleagues (1990). Self-report measures are more sensitive and reliable when children are able to cooperate and provide verbal

responses. Reliance on behavioral cues, especially in older children, may lead to an underestimation of pain intensity. The data clearly demonstrate the limitations of the respective measures in relationship to the period of postoperative recovery and emphasize the need to select the most sensitive and reliable pediatric pain assessment tools depending on the setting (e.g., PACU and Day Surgery) or clinical condition of the patient.

One concern with using a new analgesic in any population is the issue of side-effects. NSAID's have been shown to effect platelet aggregation and can increase the potential for postoperative bleeding (Conrad et al., 1988; Greer, 1990; Roe et al., 1981; Spowart et al., 1988). Although administration of ketorolac has been associated with a prolonged bleeding times in both adults and children (Bean et al., 1992; Conrad et al., 1988; Greer, 1990), it seems to be of little clinical significance, since bleeding times remain within normal and acceptable limits, return to normal in 24 hours, and do not predispose patients to an increased risk of postoperative bleeding. The findings of this study suggest that in healthy children, who do not have an underlying bleeding disorder, a single IM injection of ketorolac, given at the completion of surgery, does not cause an increase in postoperative bleeding following tonsillectomy, with or without adenoidectomy. This finding is especially notable in the population studied, since bleeding is a major concern with this particular type of surgery.

Adequate postoperative pain management has the potential to improve

patient outcomes by providing sufficient analgesia without increasing complications. In an ambulatory surgery setting, a clinically significant outcome variable is length of time until discharge home. While several factors besides, inadequate pain control, can influence discharge time (e.g., emesis, poor oral intake), the children in both groups were relatively homogeneous with respect to the occurrence of these clinical problems (unpublished clinical observations), therefore a significant finding of this study is that a single IM dose of ketorolac decreases the total length of stay by approximately 30 minutes. However, when the length of stay in the PACU was compared between the two groups, no significant differences in the total number of minutes were observed. In Day Surgery, children in the ketorolac group were discharged 25 minutes earlier than children in the saline group. Although this difference was not statistically significant, it demonstrates that the largest decrease in length of stay occurred in the Day Surgery area. The cost-effectiveness of ketorolac and the clinical and economic significance of decreasing the length of stay in ambulatory surgery needs to be evaluated in the context of current billing practices for ambulatory surgery services, which vary across institutions, from charges accrued by the minute, to a comprehensive fee based on the type of the procedure being performed.

Nursing Implications

Nurses have a major responsibility for both accurate assessment and pharmacologic management of postoperative pain in children. It is important for

nurses to understand the developmental considerations and situational factors which influence the selection of the most appropriate pain intensity measure for children. The findings from this study highlight the potential advantages and limitations of both self-report and behavioral pain intensity measures in obtaining an accurate assessment of pain intensity in children undergoing ambulatory surgery.

It is anticipated that the findings of this study will contribute to nurse's understanding and knowledge of the analgesic efficacy of both ketorolac and fentanyl in children following tonsillectomy, and advance nurses recognition of the potential benefit of combining analgesics with different mechanisms of action, to achieve optimal pain relief in the children that they care for.

Finally, the findings of this study illustrate the importance of objectively evaluating the incidence and severity of drug-induced side-effects. Concerns regarding the potential for an increased risk of postoperative bleeding associated with ketorolac have hindered the clinical use of this analgesic. However, the data from this study suggest that there is no increase in postoperative bleeding following a single IM dose of ketorolac, given at the completion of surgery, in children following tonsillectomy, with or without adenoidectomy.

Conclusions

The following conclusions can be made from this study:

1. A single IM dose of ketorolac, given at the completion of surgery,

decreased the total postoperative fentanyl dose requirements in children following tonsillectomy, with or without adenoidectomy, by 26%.

2. A single IM dose of ketorolac, given at the completion of surgery, shortened the length of stay in ambulatory surgery for children following tonsillectomy, with or without adenoidectomy, by 30 minutes.

3. A single IM dose of ketorolac, given at the completion of surgery, does not increase the severity or duration of postoperative bleeding in children following tonsillectomy, with or without adenoidectomy.

4. Behavioral pain intensity measures are more appropriate pain assessment tools in the immediate postoperative period (i.e., PACU) than self-report pain intensity measures.

5. Fentanyl is an effective analgesic, albeit an analgesic of short duration, in the postoperative management of pain associated with tonsillectomy, with or without adenoidectomy.

Recommendations

Recommendations for future investigations include:

1. Evaluation of the effectiveness of a pretreatment regimen using NSAID's preoperatively or intraoperatively, for patients having surgical procedures that produce at least moderate postoperative pain (i.e., pre-emptive analgesia).

2. Comparison of different doses of ketorolac to determine the dose-response relationship relative to pain intensity, clinical onset of pain, and the incidence and severity of postoperative swelling.

3. Evaluation of different doses of fentanyl administered in the postoperative period to determine if analgesic efficacy can be enhanced without an increase in side-effects.

4. Investigation of alternative routes of administration for ketorolac.

5. Development and refinement of more sensitive behavioral measures with application to postoperative patients.

6. Replication of this investigation as a double-blind study, to compare the efficacy of various combinations of NSAID's, intraoperative opioid, and/or local anesthetic administration.

7. Investigations to compare the efficacy of various combinations of NSAID's and postoperative opioids.

8. Evaluation of other opioid analgesics with a longer half-life (e.g., morphine sulfate) for postoperative pain management in ambulatory surgery.

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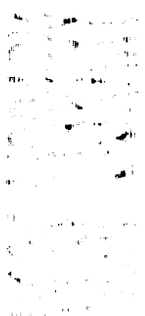


APPENDIXES

APPENDIX A

Patient/Family Information Sheet

Patient I.D. #: ____

PATIENT/FAMILY INFORMATION SHEET

---

1. Circle the total number of brothers and sisters:

   0 1 2 3 4 5 6 7 8 9

2. Was this child born: 1st 2nd 3rd 4th 5th 6th 7th 8th 9th

3. Why is your child having his/her tonsils out?

   (1) Recurrent Tonsillitis/Infection
   (2) Sleep Apnea/Obstructive Airway
   (3) Other (please specify)

4. If your child is having his/her tonsils out for recurrent tonsillitis, when was his/her most recent episode of tonsillitis:

   (1) $\leq$ 2 weeks
   (2) 3-4 weeks
   (3) > 1 month
   (4) Not applicable

5. Does your child have any history of bleeding problems?

   (1) Yes ___ (2) No ___

   If yes, what kind of problems: _____

6. Does your child have any allergies to medications?

   (1) Yes ___ (2) No ___

   If yes, to what medications: _____

7. Circle the highest grade or year completed by the child's mother in regular school, vocational school, college, or graduate professional training:

Grade School								High School			
1	2	3	4	5	6	7	8	9	10	11	12

College				Graduate School						
13	14	15	16	17	18	19	20	21	22	>22

8. Circle the highest grade or year completed by the child's father in regular school, vocational school, college, or graduate professional training:

Grade School								High School			
1	2	3	4	5	6	7	8	9	10	11	12

College				Graduate School						
13	14	15	16	17	18	19	20	21	22	>22

9. Circle the number that best describes the ethnic background of the child's mother:

1 American Indian
2 Asian or Pacific Islander
3 Black
4 Caucasian/White
5 Hispanic
6 Mixed Ethnic Background
7 Other (specify) _____

10. Circle the number that best describes the ethnic background of the child's father:

1 American Indian
2 Asian or Pacific Islander
3 Black
4 Caucasian/White
5 Hispanic
6 Mixed Ethnic Background
7 Other (specify) _____

11. Circle the number that best describes your gross annual household income:

1	≤ $10,000.00
2	$10,001.00 - $20,000.00
3	$20,001.00 - $30,000.00
4	$30,001.00 - $40,000.00
5	$40,001.00 - $50,000.00
6	$50,001.00 - $60,000.00
7	$60,001.00 - $70,000.00
8	$70,001.00 - $80,000.00
9	> $80,000.00

12. Is there any history of pain problems in your family?

(1) Yes ___ (2) No ___ (3) Unsure ___

If so, would you please give a brief description?

_____
_____
_____

13. What would you describe as your child's most painful experience?

_____
_____
_____

14. Do you think your child will have difficulty coping with pain following surgery?

(1) Yes ___ (2) No ___ (3) Unsure ___

If yes, in what way?

_____
_____
_____

15. Has your child ever been hospitalized before?

(1) Yes ___ (2) No ___ (3) How many times: ___

Reason for hospitalization:

_____
_____
_____

16. Has your child ever had surgery before?

(1) Yes ___ (2) No ___ (3) How many times: ___

If yes, what type(s) of surgery?

_____
_____
_____

APPENDIX B

Medical Record Review Form

Patient I.D.: ____

Date: _____

MEDICAL RECORD REVIEW DATA

Patient Medical Record #: _____

Date of Birth: _____

Age (months): _____

Weight (kg): _____

Sex: (1) Male (2) Female

ASA Level: I II III IV

Type of Current Surgical Procedure:

(1) Tonsillectomy
(2) T&A
(3) Tonsillectomy/BMT
(4) T&A/BMT
(5) T&A/RMT
(6) T&A/BMT/Frenulectomy
(7) T&A/LMT
(8) T&A/Frenulectomy
(9) T&A/Tooth Removal

Indication for Surgery:

(1) Tonsillitis
(2) Apnea/Obstructive Airway
(3) Tonsillitis/Otitis Media
(4) Tonsillitis/Apnea/Otitis Media
(5) Apnea/Otitis Media
(6) Tonsillitis/Apnea

Surgeon:

(1) Moore
(2) Fortson
(3) Heiner
(4) Singh
(5) Ballecer
(6) Lanier
(7) Rocha

Anesthesiologist:

(1) Greaves
(2) Rajagopalan
(3) Farrell
(4) Cramolini
(5) Airola
(6) Hansen
(7) Morton
(8) Birek
(9) Fernandez
(10) Voora

Pre-Op Hemoglobin: ____

Pre-Op Hematocrit: ____

Pre-Op Platelets: ____

Pre-Op PT: ____

Pre-Op PTT: ____

Pre-Op Heart Rate: ____

Pre-Op Systolic Blood Pressure: ____

Pre-Op Diastolic Blood Pressure: ____

Pre-Op MAP: ____

Pre-Op Respiratory Rate: ____

Pre-Op Sedation Score: _____

Type of Anesthesia:

(1) Inhalation - Halothane/Oxygen
(2) Inhalation - Halothane/Nitrous Oxide/Oxygen
(3) Inhalation - Isoflurane/Oxygen
(4) Inhalation - Isoflurane/Nitrous Oxide/Oxygen
(5) Inhalation - Halothane/Isoflurane/Nitrous Oxide/Oxygen

Intra-Operative Medications:

Droperidol Yes __ No __

Atropine Yes __ No __

Decadron Yes __ No __

Propofol Yes __ No __

Versed Yes __ No __

Robinol Yes __ No __

Hydroxyzine Yes __ No __

Metoclopromide Yes __ No __

Other _____

Anesthesia Start Time: ____

Anesthesia Stop Time: ____

Total Anesthesia Time: ____

OR Start Time: ____

OR Stop Time: ____

Total OR Time: ____

Estimated Blood Loss (cc's): ____

Surgical technique for removal of tonsils/adenoids:

Blunt Dissection Yes ___ No ___

Electrocautery Dissection Yes ___ No ___

Hemostasis Technique:

Suture ligation Yes ___ No ___

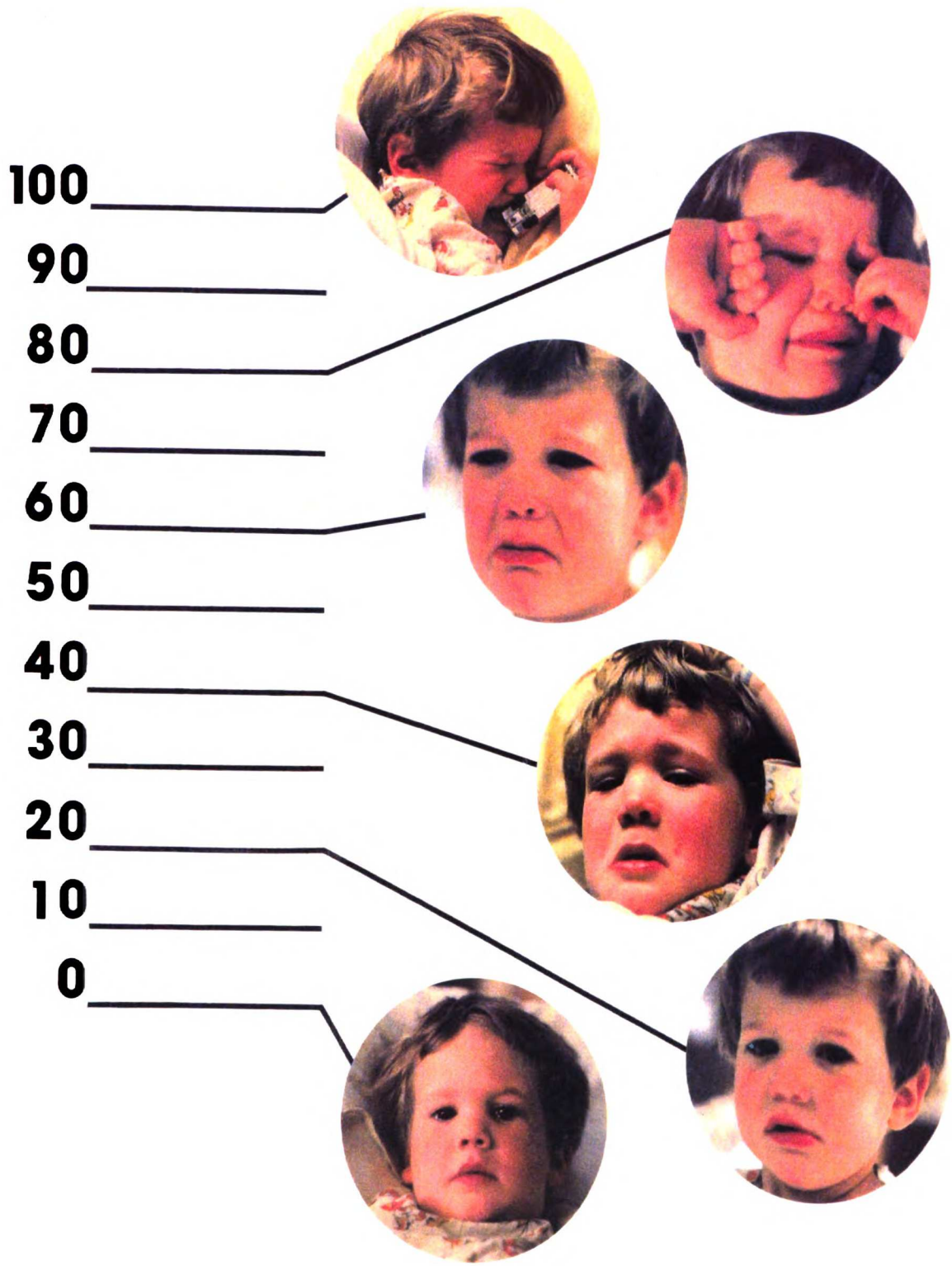
Electrocautery Yes ___ No ___

Nasopharyngeal/Adenoid Pack Yes ___ No ___

APPENDIX C

The Oucher

OUCHER! ©1983



APPENDIX D

The CHEOPS

Behavioral Definitions and Scoring of CHEOPS

Item	Behavior	Score	Definition
Cry	No Crying	1	Child is not crying.
	Moaning	2	Child is moaning or quietly vocalizing, silent cry.
	Crying	2	Child is crying, but the cry is gentle or whimpering.
	Scream	3	Child is in a full-lunged cry; sobbing; may be scored with or without complaint.
Facial	Composed	1	Neutral facial expression.
	Grimace	2	Score only if definite negative facial expression.
	Smiling	0	Score only if definite positive expression.
Child Verbal	None	1	Child is not talking.
	Other complaints	1	Child complains, but not about pain, e.g., "I want to see mommy" or "I am thirsty."
	Pain complaints	2	Child complains about pain.
	Both complaints	2	Child complains about pain and about other things, e.g., "It hurts; I want mommy."
	Positive	0	Child makes any positive statement or talks about other things without complaint.
Torso	Neutral	1	Body (not limbs) is at rest; torso is inactive.
	Shifting	2	Body is in motion in a shifting or serpentine fashion.
	Tense	2	Body is arched or rigid.
	Shivering	2	Body is shuddering or shaking involuntarily.
	Upright	2	Child is in a vertical or upright position.

Touch	Not touching	1	Child is not touching or grabbing at wound.
	Grab	2	Child is grabbing vigorously at wound.
	Restrained	2	Child's arms are restrained.
Legs	Neutral	1	Legs may be in any position but are relaxed; includes gentle swimming or serpentine-like movements.
	Squirming/ kicking	2	Definite uneasy or restless movements in the legs and/or striking out with foot or feet.
	Standing	2	Standing, crouching, or kneeling.
	Restrained	2	Child's legs are being held down.

APPENDIX E

Grading Scale for Postoperative Bleeding

Grading Scale for the Severity of Postoperative Bleeding

0 - No observed bleeding

1 - Mild bleeding, small amount of blood in nares or from mouth

2 - Moderate bleeding requiring pseudophedrine nose drops or other intervention

3 - Severe bleeding necessitating return to the operating room

APPENDIX F

Parental Consent Form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Parental Consent for Child to be a Research Subject

Purpose and Background

Dr. Christine Miaskowski and Kim Sutters, RN, MSN, from the Department of Physiological Nursing, University of California, San Francisco, and Dr. Theodore Greaves, from the Department of Anesthesiology, Valley Children's Hospital, are conducting a study to determine ways to help children when they have pain. They are trying to learn about the different effects of the medications that are given to children to help take the pain away. Because my child will be having an operation, he/she is asked to participate in this study.

Procedures

If I decide to permit my child to help with this study, the following will happen:

1. My child will be randomly assigned to Group A (given an injection of normal saline at the end of the operation while my child is still asleep and given intravenous doses of Fentanyl after surgery to relieve pain) or Group B (given an injection of Ketorolac at the end of the operation while my child is still asleep and given intravenous doses of Fentanyl after surgery to relieve pain). This means that my child has approximately a 50/50 chance of being in either group;

2. My child will be asked to have his/her breathing, heart rate, and blood pressure closely monitored by several recorders placed at the bedside;

3. My child will be asked to choose a number or a picture that represents how much pain he/she is experiencing;

4. My child will have his/her behavior observed for signs of pain;

5. My child will be observed for signs of bleeding.

The monitors will be placed on my child after surgery when he/she returns to the recovery room and will remain in place until my child goes home. They will record my child's breathing, oxygen and carbon dioxide levels, heart rate, and blood pressure. When it is determined by my child's nurse that he/she should receive some pain medication, my child will be asked to report how much pain he/she has before the medication is given and then again 5 minutes after the medication is given. This same procedure will be done every 30 minutes while my child is in the recovery room, each time that my child receives medication for pain following surgery, and then every hour until my child goes home.

Risks/Discomforts

1. **Randomization:** The medication group that my child is assigned to may later be shown to be less effective or beneficial than the other group.

2. **Monitors:** Because the probe for one of the monitors is heated, my child may develop a small red area on his/her skin that usually goes away after a few hours. It is also possible that he/she may develop some skin irritation from the adhesive when the patch for the monitor is removed.

3. **Ketorolac:** There may be an increased risk for bleeding associated with this medication.

4. **Confidentiality:** Participation in research will be handled as confidentially as possible within the law. All of my child's research records will be coded with a number and kept in a locked cabinet. Only the study investigators will have access to my child's records.

Treatment and Compensation for Injury

If my child is injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, I may call the office of the Committee on Human Research at (415) 476-1814.

Benefits

Randomization: The medication(s) that my child is assigned to receive may later be shown to be more effective or beneficial. However, this cannot be guaranteed. It is hoped that the information obtained from this study may help in the treatment of other children who experience pain.

Alternatives

If I choose not to have my child participate, his/her care will not be affected and pain medication will be provided as ordered by his/her physician.

Costs

I will not be charged for any of the study procedures, monitors, or drugs. All study costs will be paid by the investigators. I will be responsible for all costs not related to the study procedure.

Reimbursement

I will not be reimbursed for my child's participation in this study.

Questions

This study has been explained to me by Kim Sutters, RN, MSN or one of her associates, and my questions were answered. If I have any other questions about the study, I may call Dr. Christine Miaskowski at (415) 476-9407, Kim Sutters at (209) 226-7044, or Dr. Greaves at (209) 229-9571.

Consent

I have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep. Participation in this research is voluntary. I have the right to decline to participate or to withdraw at any point in this study without jeopardy to my child's medical care. If I wish to have my child participate, I should sign below.

_____ _____

Date Parent's Signature

_____

Person obtaining consent

APPENDIX G

Child Assent Form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Assent for Child to be a Research Subject

Dr. Christine Miaskowski and Kim Sutters, RN, MSN from the Department of Physiological Nursing, University of California, San Francisco, and Dr. Theodore Greaves, Chief of Anesthesiology, Valley Children's Hospital, are conducting a study to determine ways to help children when they are hurting. They are trying to learn about the different effects of the medicines that are given to children to help take the hurt away. Because I will be having an operation, I am being asked to help with this study.

If I decide to help with this study, these things will happen:

1. I will be given some medicine after my operation to help me when I am hurting, or I will be given one kind of medicine when I am asleep for my operation and a different medicine after my operation to help me when I am hurting;

2. I will have my breathing, heart rate, and blood pressure closely watched by several machines put by my bedside until I go home;

3. I will be asked to choose a number or a picture that shows how much I am hurting;

I will be asked to do each of these things before I receive the medicine to help my hurt go away, and then again 5 minutes after I receive my medicine. I will also be asked to choose a number or a picture that shows how much I hurt every 30 minutes while I am in the wake-up room, and then every hour until I go home.

Because the probe for one of the monitors is heated, it may cause a small red mark on my skin that usually goes away after a few hours. It is also possible that the tape from the sticky patch may cause a red mark on my skin when it is taken off. One of the medicines may cause some bleeding.

The medicine(s) that I get may help me more when I am hurting. Also, what we learn from the study may help other children who are hurting after their operation. When I sign my name on this paper, it means that I want to be in the study. I will still be given medicine to help me when I am hurting, even if I do not want to be in the study.

If I have any questions, I may call Christine Miaskowski at the School of Nursing at (415) 476-9407 between 9 a.m. and 5 p.m. Monday through Friday, Kim Sutters at (209) 226-7044, or Dr. Greaves at 229-9571. I have been given a copy of this consent form and a copy of the Experimental Subject's Bill of Rights.

Date: _____ Child: _____

Investigator: _____

APPENDIX H

Data Collection Sequence

DATA COLLECTION SEQUENCE

Preoperative/Baseline	Intraoperative
* Consent/assent obtained * Instructed in the use of the Oucher * Randomized to treatment group A. Saline B. Ketorolac	* Inhalation anesthesia (i.e., nitrous oxide, oxygen, isoflurane and/or halothane) * No intraoperative local anesthetic * No intraoperative opioid * Study drug given at the completion of surgery, before returning to PACU

Immediate Postoperative/PACU	Postoperative/Day Surgery
* Arrival in PACU measures 1. CHEOPS 2. Postoperative bleeding * Pre- and post-fentanyl measures for each dose administration time 1. Oucher 2. CHEOPS 3. Postoperative bleeding * Measures as above every 30 minutes in the PACU, if no fentanyl given * Measures as above repeated at discharge from PACU	* Pre- and post-drug measures A. Fentanyl (5 minutes) B. Tylenol or Tylenol with codeine (30 minutes) * Hourly measures 1. Oucher 2. CHEOPS 3. Postoperative bleeding * Measures as above repeated at the time of discharge home