Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children

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A randomized, double-blind, prospective study was performed to determine the effects of perioperative administration of morphine or methadone on postoperative analgesic requirements and pain scores in 35 children aged 3 to 7 years undergoing major surgery. After a standardized induction of anesthesia, methadone or morphine, 0.2 mg/kg, was blindly administered, and supplemental doses were titrated to achieve comfort in the recovery room. Pain was assessed during the next 36 hours with a combination of validated behavioral and self-report measures. Patients in the methadone group required fewer supplemental opioid analgesic drugs during the next 36 hours, and reported lower pain scores. No patient had prolonged emergence from anesthesia, and no patient required naloxone or postoperative ventilatory assistance. No major adverse events occurred. We conclude that perioperative intravenous administration of methadone is an effective, inexpensive, and technologically simple means for providing prolonged analgesia for children after surgery. (J PEDIATR 1991;119:136-41)

Epidemiologic studies suggest that children frequently receive inadequate analgesia after surgery.[1-4] The traditional method of providing postoperative analgesia for children involves intramuscular injection of opioid analgesics such as morphine and meperidine. Methods of analgesia that diminish or eliminate the need for intramuscular injections would be useful, because these injections frequently generate fear and anxiety. Postoperative analgesia is best begun intraoperatively, to provide a smooth emergence from anesthesia and a calm recovery room course. The clinical impression that pain is more easily prevented than treated has been substantiated by investigation of the prolonged effects of opioid premedication and intraoperative regional blockade on subsequent analgesic requirements.[5,6]

One convenient method of providing prolonged postoperative analgesia that has been studied in adults is the administration of a single large dose of the opioid analgesic methadone at the beginning of anesthesia and surgery. Methadone is a synthetic opioid analgesic that has a rapid distribution phase but very prolonged elimination.[7] Gourlay et al.[7,8] found that more than half of adult patients receiving an intraoperative methadone dose of 20 mg required no

ACCS	Analogue Continuous Chromatic Scale
ANOVA	Analysis of variance
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale

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supplemental analgesics other than paracetamol (acetaminophen) for their entire perioperative course, and those patients who required opioids averaged 17 hours before their first supplemental injection. Although all patients in the original studies were easily awakened after surgery, a few patients were found later to have somnolence or delayed tracheal extubation with this dose; some investigators have recommended a smaller initial loading dose followed by titration to comfort on awakening. Previous pediatric studies from our group have shown that methadone has a long elimination half-life (mean 19 hours) in children[9] and that titrated loading doses of methadone during the first 12 hours after scoliosis surgery reduce analgesic requirements for the next 24 hours.[10]

Analgesic studies in younger children have been hampered by the difficulties of pain assessment.[11] Children less than age 7 years are generally not adept at pain rating by standard visual analogue scales. Recently, self-report and behavioral pain assessment measures have been devised and validated for children aged 3 to 7 years.[12-14] We designed a randomized, prospective, double-blind trial to address the following questions: (1) Does methadone diminish subsequent analgesic requirements relative to morphine, administered by a similar algorithm? (2) Is this method of administration safe? (3) Does methadone administration result in diminished pain scores relative to morphine? (4) Finally, what is the degree of agreement between self-report and behavioral measures of pain intensity in this setting? Questions 1 to 3 are addressed in this report; question 4 is the subject of a separate report.[15]

METHODS

Subjects. The sample consisted of 35 subjects who met the following criteria: (1) boys or girls 3 to 7 years of age, (2) English-speaking children, (3) scheduled for major surgery for which significant postoperative pain could be expected, (4) had surgery of at least 90 minutes' duration involving the back, thorax, abdomen, pelvis, or extremities, and (5) able to provide self-reports of pain intensity by using the selected research instruments.

Children were excluded from the sample if there was evidence on history and physical examination (or, when indicated, on screening laboratory studies), suggesting (1) severe liver dysfunction (bilirubin level >2.0 mg/dl; 34 mmol/L) or renal dysfunction (creatinine concentration >1.5 mg/dl; 132 μmol/L), (2) neurologic or psychiatric disturbances, developmental delay, or learning disabilities, (3) chronic opioid administration, or (4) allergy to any opioid.

Parents gave informed consent according to procedures approved by the Children's Hospital Committee on Clinical Investigation, and patients received instruction regarding the pain assessment tools at the time of their visit to the preoperative clinic, typically 1 to 4 days before surgery. Instruction in use of the instruments was provided in a standardized fashion by study investigators.

Study design

Randomization. After enrollment, patients were assigned randomly to one of two groups (methadone and morphine groups) by a pharmacist using a random-numbers table. Patients, parents, physicians, and nurses were unaware of the assignments.

Perioperative management. To minimize variations in analgesic or sedative effect caused by anesthetic agents, we standardized drugs for maintenance of anesthesia. Induction proceeded via intravenous thiopental, rectal methohexital, or inhaled nitrous oxide–halothane administration according to clinical indications. Thereafter, in all cases, anesthesia was maintained with nitrous oxide (60 to 70 vol% in oxygen) and isoflurane, 0 to 1 vol% end-tidal concentration, as indicated by clinical signs. Curare was used for neuromuscular blockade. After tracheal intubation and before incision, anesthesiologists administered 0.2 mg/kg of the study drug (morphine or methadone) intravenously from a blinded vial. No other opioids and no sedative-hypnotics or neuroleptics were administered intraoperatively.

Recovery room management. After emergence from anesthesia, patients were transported to the recovery room. Nurses administered the same study analgesic (morphine or methadone) from blinded vials in increments of 0.05 mg/kg intravenously every 10 minutes until patients appeared comfortable and adequately alert. They were transferred to the postoperative ward approximately 1 hour after the last opioid dose.

Analgesic administration on the postoperative wards. Nurses on the postoperative wards initially administered morphine, 0.1 mg/kg intramuscularly every 3 hours as needed, on the basis of their customary interpretations of patient reports and behavioral signs of distress. Once oral solids were tolerated, they administered acetaminophen, 10 mg/kg orally every 3 hours, and codeine, 1 mg/kg orally every 3 hours as needed. Nurses, physicians, patients, and parents were unaware of group assignments and were also unaware of formal pain assessments performed by the study investigators.

Patient assessments on the postoperative wards. Pain intensity was assessed by study investigators using the Oucher,[12] the Analogue Continuous Chromatic Scale,[13] and the Children's Hospital of Eastern Ontario Pain Scale[14] measures (see below). Two pain-intensity measures were obtained by self-report (Oucher and ACCS), and one was based on behavioral observation (CHEOPS). Pretest measures of self-reported pain intensity and observer ratings of pain behaviors were obtained before surgery. Posttest mea-

Table I. Group differences

	Group		Significance	
	Methadone (n = 18)	Morphine (n = 17)	*t*	*p*
Age (yr)	5.6 ± 1.6	5.4 ± 1.5	1.1*	0.73
Previous surgical procedures	1.1 ± 1.4	1.0 ± 2.2	0.18*	0.869
Previous hospitalizations	1.4 ± 1.7	1.5 ± 3.1	−0.03*	0.975
Opioid doses				
Operative day	0.72 ± 0.83	1.35 ± 0.99	4.2†	0.049
First postoperative day	3.28 ± 1.53	4.47 ± 2.12	3.7†	0.059

Group differences in demographic variables and in opioid dosing are presented. Values (except significance) are expressed as mean ± SD.
*Two-tailed Student *t* statistic.
†One-way ANOVA statistic.

sures of the same kind were obtained every 2 hours while the child was awake for the first 36 hours after surgery. The persons who collected the pain data, as well as the patients, parents, nurses, and physicians, were unaware of which children were in the treatment and control groups.

The Oucher is a posterlike device with a numeric scale on the left for older children and a photographic scale on the right for younger children. The photographs are of one 4-year-old child and are placed in what appears to be increasing levels of discomfort. Studies on the Oucher have provided evidence to support the content, construct, discriminant, and convergent validity of the photographic scale. In particular, responses to analgesic administration are appropriate, and the scale appears to discriminate pain from a measure of hospital fear. The ACCS is a slide-rule type of device on which subjects indicate the amount of their pain by moving a sliding marker on a color scale from pale pink to dark red. The darker the color, the greater the pain. A 10 cm ruler is printed on the opposite side of the device, so that subjects' self-reports in color can be converted directly into numeric scores. It has been shown that ACCS scores converge with those of a visual analogue scale in adults. For the CHEOPS, raters provided scores for a child's pain behaviors on the basis of observations made in six specific areas: cry, facial and verbal responses, and movement in the arms, legs, and torso.

Children were asked to provide scores every 2 hours while awake for the first 36 hours after surgery. Ethical considerations prohibited awakening sleeping children to perform pain scores. Immediately before these reports, the child was rated on behavioral responses by the research assistant. These observations began within 2 hours after the termination of anesthesia. Analgesic data were verified from the medication records from the operative day to the second postoperative day.

Additional measures. Nurses recorded vital signs and level of consciousness every 4 hours and respiratory rate every 2 hours. Side effects (e.g., vomiting, pruritus) were recorded whenever they were noted.

Statistical analyses. Differences among groups were examined with a *t* test, analysis of variance, repeated-measures analysis of variance, or chi-square analysis, as appropriate. Correlation analysis and general linear models were employed to examine the effects of variables such as age and the duration and type of surgery on the observed group differences. A p value of <0.05 was considered significant.

RESULTS

Sample characteristics. Thirty-five 3- to 7-year-old children (mean age, 5.5 years; SD, 1.6) completed the study. Twenty-one children (60%) were girls. Nine (26%) did not attend any form of school or day care, four (11%) attended day care, five (15%) attended preschool or nursery school, and 17 (48%) attended primary school grades ranging from kindergarten to second grade.

Nine children (26%) had osteotomies of the limbs or hips, 15 (43%) had ureteral reimplantation, six (17%) had various major general surgical procedures (such as repair of the pectus excavatum), and five (14%) had various orthopedic procedures other than osteotomies. The average length of procedures was 3.8 hours (range 1.9 to 6.3 hours).

Fifteen children (43%) had never been hospitalized previously. In addition, 15 (43%) had had from one to nine previous operations. Sixteen subjects (46%) were enrolled in the study during their visit to the preoperative clinic, and 19 after their admission to the hospital 1 or more days before surgery.

As shown in Table I, 17 children were assigned to the control group and 18 to the experimental group. No significant differences were found between the two groups in average age, number of previous hospitalizations, or surgeries. Using chi-square analysis, we found no differences between the two groups in gender or in type of surgery. There were

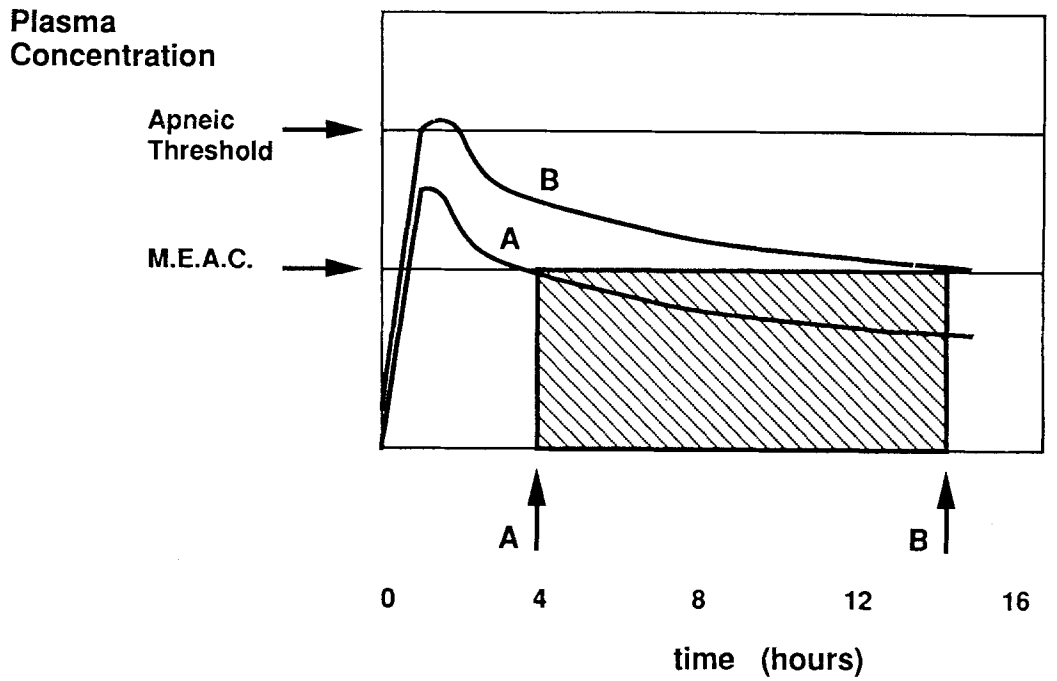

Figure. Methadone undergoes rapid distribution but prolonged elimination from circulation. These theoretic curves depict marked dependence of duration of analgesia on magnitude of perioperative loading dose. In *curve A*, plasma level is only slightly above minimal effective analgesic concentration *(M.E.A.C.)* at end of distribution phase, and result is shorter duration of analgesia, roughly 4 hours. Increasing magnitude of loading dose by only 25% *(curve B)* could result in duration of analgesia as long as 14 hours.

no differences between groups in the number of supplemental analgesic doses required in the recovery room.

Postoperative analgesic requirements. The control group received more supplemental opioid doses than the experimental group on the operative day (ANOVA, $F = 4.2$, $p = 0.049$; Table I). On the first postoperative day, the difference did not reach statistical significance. (ANOVA, $F = 3.7$, $p = 0.059$). Children received between 1 and 17 doses of opioids during the first 2 days postoperatively. On the operative day, the control group received more injections than the experimental group (means = 1.29 and 0.72, respectively; $p = 0.03$).

Pain scores. Oucher and ACCS scores (both self-report measures) showed excellent agreement for all time points. If scores at all periods are grouped together (ignoring independence considerations), the correlation coefficient between the Oucher and ACCS scores was 0.91 (identical for Pearson and Spearman scores). Conversely, there was very little relationship between the Oucher and ACCS scores and the CHEOPS scores (behavioral measure). The correlation between CHEOPS and Oucher scores over all time points was 0.30 (Pearson) or 0.19 (Spearman), and the correlation between the CHEOPS and ACCS scores over all time points was 0.25 (Pearson) or 0.13 (Spearman). As described in greater detail earlier,[15] CHEOPS scores tended to show little fluctuation and underestimated pain intensity relative to the two self-report measures.

The overall trend of pain scores for both ACCS and Oucher decreased with time after surgery, with wide variation in the two groups. Repeated-measures ANOVA applied to pain scores was limited by missing values when children were sleeping or unwilling to answer. For the four periods for which there were no missing data, results showed that mean pain scores were lower in the methadone group for each period ($p < 0.05$). If pain scores were grouped together for the entire observation period, the differences were statistically and clinically significant. For example, if ACCS scores at all time points are subcategorized for heuristic purposes as mild-moderate (<50) or severe (≥ 50), then during the 3 days of observation there were almost twice as many severe pain scores in the morphine group as in the methadone group (52/147 [35.4%] severe scores in the morphine group; 28/152 [18.4%] severe scores in the methadone group; chi-square statistic = 10.96, $p = 0.0009$).

Postoperative recovery and adverse events. There were no differences between the experimental and control groups in the following variables: (1) percentage of time observed to be sleeping, (2) type of diet tolerated 36 hours after surgery, (3) number of episodes of emesis, or (4) number of children requiring treatment for pruritus. Approximately half the

Table II. Suggested algorithm for perioperative methadone dosing

Intraoperative dosing	At induction, 0.2 mg/kg IV; reduce dose if following is true: Surgery is <90 minutes in duration Sedative-hypnotics or other opioids are given Patients have medical conditions that increase susceptibility to respiratory depression
Recovery room dosing	Administer 0.05 mg/kg every 5 to 10 min until comfort is achieved or as limited by somnolence or respiratory depression
Postoperative ward dosing	"Sliding scale" every 4 hr for 48 hr* For severe pain: 0.07-0.08 mg/kg For moderate pain: 0.05-0.06 mg/kg For minimal pain If very alert: 0.03 mg/kg If somnolent: 0 mg/kg

*All doses given via a burette for 20 minutes.

patients were confined to bed throughout the study period for surgical indications, and half the patients, including all those undergoing ureteral reimplantation, had bladder catheterization for surgical indications.

No patient in either group required naloxone, and no patient had delayed emergence from anesthesia or required postoperative ventilatory assistance. No patient had a respiratory rate less than 14 breaths/min.

Effects of age and duration of surgery. Correlation analysis and general linear modeling showed no effects of analgesic dosing on age or duration of surgery. There was a weak negative correlation of CHEOPS scores with age ($r = 0.23$; $p = 0.008$) but no correlation of Oucher or ACCS scores with age.

DISCUSSION

For institutions in which intramuscular injections of opioids remain standard, our findings suggest that children managed with perioperative methadone loading doses will be more comfortable, and will require fewer injections to remain comfortable, than patients receiving comparable doses of morphine intraoperatively. The control group in this study received what would be regarded as a large intraoperative dose of morphine by the standards frequently applied in pediatric anesthesia practice. If the control group had received an inhalational anesthetic alone or in combination with a short-acting lipophilic opioid, then it might be expected that these patients would have had much greater analgesic requirements than our morphine control group exhibited.

Studies comparing morphine with methadone in adults and older children have produced somewhat variable conclusions regarding relative analgesic duration. Because methadone has rapid distribution but very slow elimination, analgesic duration is very critically dependent on the magnitude of loading doses. Prolonged analgesia requires that the loading doses be large enough so that the plasma level remains well above the minimal effective analgesic concentration after the distribution phase is completed (Figure).

In the current study, although differences in pain scores and analgesic requirements were shown between groups, they were relatively modest and short lived. Gourlay et al.[7, 8] demonstrated very prolonged analgesia with the administration of 20 mg loading doses of methadone at anesthetic induction, but we do not recommend routine administration of analogous intraoperative doses (i.e., >0.2 mg/kg) to children because pilot studies in children aged 7 to 19 years showed an appreciable incidence (25%) of hypoventilation or somnolence at the end of surgery, when 0.3 mg/kg was administered at the beginning of surgery (Berde CB, Sethna NS: unpublished observations), particularly for operations lasting less than 90 minutes. It is thus more reasonable and conservative to limit the intraoperative dose to 0.2 mg/kg and to titrate small supplemental doses to clinical signs in the highly observed environment of a recovery room.

Alternative methods of analgesia include continuous intravenous opioid infusions, patient-controlled analgesia, epidural analgesia, and other forms of regional blockade. Continuous infusions can provide constant drug levels with an excellent safety margin, provided there is careful titration to clinical effect. In some hospitals, unavailability of infusion pumps limits wider application of this method. More elaborate methods of analgesia, such as patient-controlled analgesia and epidural analgesia, have limitations. Patient-controlled analgesia is a promising method of administration but probably is inapplicable before approximately 5 to 7 years of age,[16] and it requires an expensive apparatus. Epidural analgesia can be extremely effective and safe at all ages but requires special technical expertise for younger children and requires a system of management such as an acute pain service,[17-19] which is not available for many pediatric centers at present. In addition, epidural an-

algesia may be inapplicable for patients with abnormal spinal anatomy or in cases of surgery with incisions in cervical or cranial dermatomes.

After an initial loading procedure as described in this study, it is also possible to maintain analgesia with small supplemental doses of methadone on the postoperative ward. Small intermittent doses may be given at convenient intervals (e.g., every 4 hours) while the patient maintains a relatively constant clinical effect. A simple and conservative dosing schedule has been developed on the basis of both our study of older children and our combined pharmacokinetic and pharmacodynamic model calculations (Table II).

Further study is needed to evaluate safety and efficacy of this approach in children. Because of the long duration of action of methadone, if oversedation or respiratory depression occurs, a prolonged period of observation may be needed, and if naloxone is required, it may need to be repeated or given as an infusion for many hours. In addition, it is generally advisable to continue methadone administration for only 2 or 3 days after most surgical procedures to avoid excessive sedation associated with drug accumulation during a time of decreasing pain intensity. With these qualifications, perioperative administration of methadone should be regarded as a technologically simple alternative to continuous morphine infusions, especially in situations in which infusion pumps are not readily available.

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