A Randomized Clinical Trial of Analgesia in Children with Acute Abdominal Pain

MICHAEL K. KIM, MD, RICHARD T. STRAIT, MD, THOMAS T. SATO, MD, HALIM M. HENNES, MD, MS

Abstract. **Objective:** To evaluate the effects of intravenous morphine on pain reduction, physical examination, and diagnostic accuracy in children with acute abdominal pain. **Methods:** A randomized, double-blind, placebo-controlled clinical trial was conducted at an emergency department of a tertiary care children's hospital. Children aged 5–18 years with abdominal pain of ≤5 days' duration, pain score ≥5 on a 0–10 visual analog scale, and need for surgical evaluation were eligible. Following the initial assessment, patients were randomized to receive either 0.1 mg/kg morphine or an equal volume of saline. The pediatric emergency medicine physician and surgical consultant independently recorded the areas of tenderness to palpation and percussion, and their diagnoses before the study medication and 15 to 30 minutes later. **Results:** Sixty patients were enrolled, and 29 received morphine and 31 received saline. The demographic characteristics between the two groups were similar. The median reduction of pain score between the two study groups was 2 (95% CI = 1 to 4; p = 0.002). There was no significant change in the areas of tenderness in both study groups. Children with surgical conditions had persistent tenderness to palpation and/or percussion. There was no significant change in the diagnostic accuracy between the study groups and between the physician groups. All patients requiring laparotomy were identified and no significant complication was noted in the morphine group. **Conclusions:** Intravenous morphine provides significant pain reduction to children with acute abdominal pain without adversely affecting the examination, and morphine does not affect the ability to identify children with surgical conditions. **Key words:** analgesia; acute abdominal pain; children; pediatrics. ACADEMIC EMERGENCY MEDICINE 2002; 9: 281–287

FOR decades, analgesia was withheld from patients with acute abdominal pain in the fear of masking symptoms, changing physical findings, and ultimately delaying diagnosis and definitive surgical intervention.[1,2] This non-evidence-based teaching/practice was challenged recently by several studies that demonstrated effectiveness of opioids in providing pain relief to adult patients with acute abdominal pain without adverse effects or delay in diagnosis.[3–7] These findings have led to the recommendation for judicious use of analgesia after initial evaluation in patients with acute abdominal pain both in the surgical literature and in the clinical policy statement from the American College of Emergency Physicians.[8,9] Furthermore, the Agency for Healthcare Research and Quality (AHRQ) concluded that appropriate use of analgesics in patients with acute abdominal pain effectively decreases pain and does not interfere with diagnosis or treatment.[10] However, application of this recommendation in children with acute abdominal pain has not been studied to date. Our study objective was to examine the effect of intravenous morphine on pain reduction, physical examination, and diagnostic accuracy in children with acute abdominal pain.

From the Department of Pediatrics, Section of Emergency Medicine (MKK, HMH), and Department of Surgery, Division of Pediatric Surgery (TTS), Medical College of Wisconsin, Milwaukee, WI; and the Department of Pediatrics, University of Cincinnati and Division of Emergency Medicine (RTS), Cincinnati Children's Medical Center, Cincinnati, OH.

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Address for correspondence and reprints: Michael K. Kim, MD, Section of Emergency Medicine, Department of Pediatrics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509. Fax: 414-266-2635; e-mail: mkim@mcw.edu

METHODS

Study Design. A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the effects of intravenous morphine on pain reduction, physical examination, and diagnostic accuracy in children with acute abdominal pain. The institutional human rights review board approved this study.

Study Setting and Population. The study was undertaken at an emergency department (ED) of a

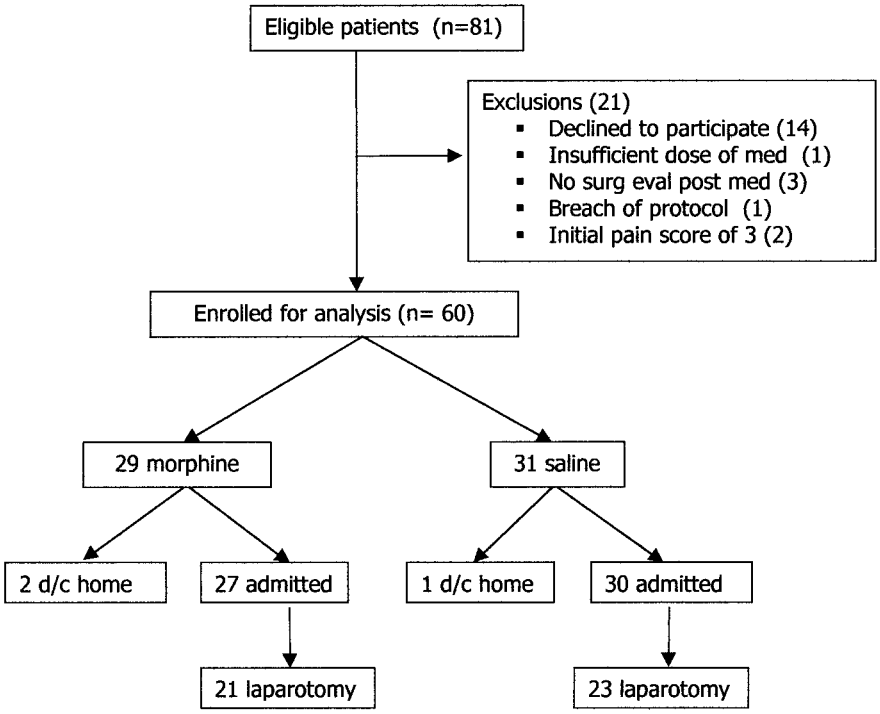

Figure 1. Overview of the eligible patients. d/c = discharged.

tertiary care children's hospital with approximately 40,000 annual visits. Children 5 to 18 years of age with abdominal pain of five days' duration or less, pain score of 5 or higher on a vertical visual analog scale (VAS), need for vascular access, and surgical consultation as determined by the pediatric emergency medicine (PEM) physician were eligible for enrollment. The VAS used was a vertical scored scale with numbers from 0 to 10 scribed in an ascending order next to each score.[11] All pain scores were assigned by the patient after the VAS was explained. Children with systolic blood pressure <90 mm Hg, allergy to morphine, suspected pregnancy, history of prior abdominal surgery, refusal of analgesia, history of sickle cell disease, or inflammatory bowel disease were excluded. Children with suspected biliary or pancreatic problems were also excluded to eliminate any bias regarding questionable effect of morphine on the sphincter of Oddi.

Study Protocol. After obtaining informed consent from the parent and assent from the patient, the pain score and the location of abdominal pain were recorded on the patient's medical record. A PEM attending or fellow (PEM physician) and the postgraduate year (PGY) I or II surgical resident (surgical consultant) independently performed and documented the physical examination and provisional diagnosis on color-coded data entry forms. Each physician was asked to mark the location of abdominal tenderness to palpation and percussion on a 3×3 table representing the nine areas of the abdomen. They also chose a prestudy medication diagnosis from a list of possible surgical and medical diagnoses provided on the data entry forms (Appendix A). For the purpose of our study, acute appendicitis (perforated and nonperforated) and bowel obstruction were considered to be surgical diagnoses and the remaining ones were considered to be nonsurgical diagnoses. Laboratory and other diagnostic tests were ordered with mutual agreement of the two physicians. However, both physicians were instructed to defer reviewing the results of any diagnostic tests until the poststudy medication assessment and data sheets were completed. Any deviation from this rule was considered a breach in protocol and the patient was excluded from final analysis.

The study medications of either 0.1 mg/kg morphine (10 mg maximum) or the same volume of normal saline were prepared in randomized clusters of 25 by the hospital pharmacist. Each syringe of study medication was labeled with the study enrollment number only, to ensure blinding. The patient's primary nurse administered the study medication, based on enrollment number, via intravenous push.

Fifteen to 30 minutes after the study medication was administered, the same physicians independently obtained the poststudy medication pain score, and repeated the physical examination. They then documented the location of abdominal tenderness to palpation and percussion, and their

final diagnosis, on the same data entry form. The attending pediatric surgeon, in conjunction with the PEM physician, determined the final disposition.

Patients admitted to the hospital were followed for complications, hospital course, and discharge diagnosis. Patients discharged home from the ED received a follow-up telephone phone call approximately 48 hours after discharge to update their conditions. They were also given a follow-up questionnaire to be completed one week after discharge from the ED inquiring about persistent abdominal pain and whether another evaluation had been made.

Measurements. The main outcome measurements for this study population were changes in pain scores, number of areas of tenderness to palpation and percussion, and the diagnostic accuracy between the morphine and saline groups. The sensitivity, the ability to correctly diagnose surgical conditions, the specificity, the ability to correctly diagnose nonsurgical conditions, and the diagnostic accuracy [(the number of patients correctly identified for laparotomy + the number correctly identified for no laparotomy)/total number] were calculated for patients in each study group.

Data Analysis and Sample Size Calculation. For nominal variables such as the pain score, the nonparametric two-group median test was used to compare the median differences in the pain scores between the two study groups. The sensitivity, specificity, and accuracy of diagnosis were also calculated for each group of physicians and study groups. Other normally distributed continuous variables were compared using the independent-sample t-test. Categorical variables were compared using the chi-square test. All analyses were performed on SPSS 10.0 (SPSS Inc., Chicago, IL), and the 95% confidence interval (95% CI) was calculated when appropriate using CIA version 1.0.[12]

Given the lack of prior research on this topic in children, we were unable to perform a reliable sample size calculation. Accordingly, we chose to study 60 children and then do a post-hoc calculation of the effect size of the primary outcome together with its 95% CI.

RESULTS

Over a 24-month period of July 1, 1998, to June 30, 2000, 81 eligible patients were approached, and 67 agreed to participate in the study. Seven of the 67 patients were excluded, leaving 60 for final analysis (Fig. 1). Twenty-nine patients were randomized to the morphine group and 31 patients to the saline group. The two study groups were similar in age, sex, ethnicity, prestudy medication median pain score, mean area of tenderness to palpation, and percussion (Table 1).

The median difference in the reduction of pain score between the two study groups was 2 (95% CI = 1 to 4; p = 0.002). Box-and-whisker plots of the pre- and poststudy medication pain score are presented in Figure 2.

The intervals between the pre- and poststudy examinations were 26.8 minutes for the morphine group and 26.2 minutes for the saline group (Δ = 0.6 minutes; 95% CI = −4.7 to 5.7).

The decrease in the mean number of areas of tenderness to palpation and percussion after morphine was statistically significant for the PEM physicians only. There was no significant change in the mean number of areas of tenderness to either palpation or percussion after morphine among

TABLE 1. Patient Characteristics of the Study Population

	Morphine (n = 29)	Saline (n = 31)	Δ (95% CI)
Demographic information and baseline median pain score			
Age—mean ± SD	11.5 ± 3.3 yr	12.2 ± 2.8 yr	0.7 (−0.9, 2.3)
Gender			
Male	16	13	0.1 (−0.1, 0.4)
Female	13	18	
Race			
White	16	24	0.2 (0, 0.5)
Nonwhite	13	7	
Median initial pain score	9	8	1 (0, 2)
Mean areas of tenderness before study medication			
Palpation (PEM*)	4.6	3.3	1.3 (−0.2, 2.7)
Percussion (PEM)	4.0	3.1	0.9 (−0.5, 2.4)
Palpation (surgical)	3.1	2.9	0.2 (−1.0, 1.4)
Percussion (surgical)	2.8	2.3	−0.5 (−0.7, 1.8)

*PEM = pediatric emergency medicine.

Figure 2. Box-and-whisker plots of pre- and poststudy medication pain scores. The horizontal line within the box represents the median pain score. The outer margins of the box represent the 25th and 75th percentile. The whiskers outside of the box represent the range of the pain scores.

TABLE 2. Mean Area of Tenderness to Palpation and Percussion in All Patients

	Mean Area of Tenderness		
	Prestudy	Poststudy	Δ (95% CI)
PEM*			
Morphine			
Palpation	4.6	3.7	0.9 (0.1, 1.8)
Percussion	4.0	3.0	1.0 (0.1, 1.9)
Saline			
Palpation	3.3	3.2	0.1 (−0.4, 0.5)
Percussion	3.1	3.0	0.0 (−0.3, 0.4)
Surgical			
Morphine			
Palpation	3.1	3.0	0.1 (−0.6, 0.7)
Percussion	2.8	2.6	0.2 (−0.1, 0.6)
Saline			
Palpation	2.9	2.6	0.3 (−0.1, 0.6)
Percussion	2.3	2.4	−0.2 (−0.7, 0.4)

*PEM = pediatric emergency medicine.

the surgical consultants. There was no significant change noted in the saline group as expected (Table 2). All 21 patients in the morphine group who required laparotomy had persistent tenderness to palpation and percussion after morphine.

Twenty-one patients (72.4%) in the morphine group and 23 patients (74.2%) in the saline group underwent exploratory laparotomy (Δ = 1.8%; 95% CI = −0.2 to 0.2). The mean durations from triage to surgery for patients in the morphine group were 7.2 hours and 6.6 hours in the saline group (Δ = 0.6; 95% CI = −1.8 to 3.0).

The discharge diagnoses of both study groups are summarized in Table 3. Six different diagnoses were entered during the enrollment in the ED: acute appendicitis, acute gastroenteritis, constipation, nonspecific abdominal pain, urinary tract infection, and mesenteric adenitis. The sensitivity, specificity, and diagnostic accuracy are presented in Table 4. The diagnostic accuracies between the PEM and surgical consultants premorphine were 21/29 and 23/29, respectively (Δ = 7.9%; 95% CI = −0.1 to 0). After morphine, there was no difference in accuracy between PEM and surgical consultants at 24/29.

Two patients in the morphine group were discharged home from the ED with diagnoses of nonspecific abdominal pain and constipation. Both reported complete resolution of their symptoms during the follow-up telephone call and in the follow-up questionnaire. One patient from the saline group was discharged home from the ED with a diagnosis of nonspecific abdominal pain, but returned three days later to be admitted for persisting symptoms. His final diagnosis was streptococcal pharyngitis and acute gastroenteritis, and he did not undergo laparotomy. Two patients with discharge diagnoses of ovarian torsion were initially diagnosed as having acute appendicitis in the ED and were considered to be surgical during the analysis.

One patient experienced nausea and another developed pruritus after receiving morphine. No other complication was observed.

Post-hoc power analysis using the improvement in diagnostic accuracy after morphine as the outcome measurement with our current sample size yielded a power of 0.18.

DISCUSSION

Our study objectives were to measure the effects of intravenous morphine on pain reduction, physical examination, and diagnostic accuracy in children with acute abdominal pain. With regard to pain reduction, our results confirmed in children what other studies demonstrated in adults, that morphine provides significant reduction of abdominal pain.[3,4]

One of the concerns in analgesia for acute abdomen is that changes in the physical examination findings may lead to delay in diagnosis. On the other hand, some believe that analgesia increases the diagnostic accuracy by increasing the patient's cooperation and permitting a better examination.[5] Studies in adults have shown a tendency for opioid analgesia to localize the area of tenderness or decrease the severity of tenderness.[3,5,6] Since the most important factor in diagnosis of surgical pathology in our patient population is peritoneal signs, we chose to use the absence or presence of percussion tenderness as the single most important examination finding. Although there was significant reduction in the mean number of area of tenderness for PEM physicians, the surgical consultants did not report any significant reduction.

We assume this difference is due to variation in the clinical assessments of different physicians. Most importantly, our findings suggest that tenderness to palpation or percussion after morphine remains, preserving the ability to evaluate the abdomen for peritoneal signs in those with surgical conditions.

To address the effect of morphine on diagnostic accuracy, we chose to assign sensitivity and specificity to the ability of pre- and poststudy medication diagnoses to predict the need for laparotomy. There were two main reasons for our method. First, determining whether a patient requires an urgent surgical intervention is the most critical decision to be made in the ED. Second, most cases of acute abdomen represent pathology in evolution such that the critical clinical findings for diagnosis may not develop until hours or days later. The diagnostic sensitivity was not adversely affected by morphine. Interestingly, the higher specificity in the morphine group by both physician groups suggests that morphine may help in identifying those children with nonsurgical causes of acute abdominal pain. To the best of our knowledge, this finding has not been reported to date. Furthermore, there was no significant change in the pre- and poststudy diagnostic accuracy between the study groups, suggesting that intravenous morphine does not significantly alter the diagnostic accuracy for both groups of physicians.

Delay in definitive surgical intervention was another concern raised in the past. However, the times to operating room for those requiring laparotomy in our study were very similar between the morphine and saline groups, supporting that morphine does not delay definitive surgical intervention.

TABLE 3. Final Diagnoses

Diagnosis	Morphine Group n = 29 (21)*	Saline Group n = 31 (23)*	Total n = 60 (44)*
Acute appendicitis	9 (9)	14 (14)	23 (23)
Acute appendicitis, perforated	8 (8)	4 (4)	12 (12)
Nonspecific abdominal pain	7 (2)	5	12 (2)
Constipation	1	1	2
Ovarian torsion	0	2 (2)	2 (2)
Ovarian cyst	0	1 (1)	1 (1)
Spontaneous peritonitis	1 (1)	0	1 (1)
Pelvic inflammatory disease	1 (1)		1 (1)
Appendiceal mass	0	1 (1)	1 (1)
Mesenteric adenitis	0	1 (1)	1 (1)
Henoch-Schönlein purpura	1	0	1
Streptococcal pharyngitis	1	1	2
Urinary tract infection	0	1	1

*In parentheses are the numbers of patients who underwent laparotomy.

In our study, we chose to use morphine because no other analgesic agents have proven to be clinically superior in relieving pain.[13] Morphine also has been the analgesic agent of choice for many clinical situations for its well-published reliability, safety, predictability, duration of action, and cost.[13] An abstract by Garyfallou and colleagues studied fentanyl in 41 adult patients, resulting in significant pain reduction without changes in examination or diagnosis.[7] Fentanyl may have some benefit over morphine due to its shorter half-life, returning patients to baseline state sooner than morphine for frequent serial examination. However, beyond ED evaluation, fentanyl may not be ideal because of need for frequent administration and higher cost.

Previous studies using various opioid analge-

TABLE 4. Diagnostic Sensitivity, Specificity, and Accuracy

	Morphine (n = 29)	Saline (n = 31)	Δ in % (95% CI)
PEM prestudy			
Sensitivity	20/21 (95.2%)	23/23 (100%)	4.8% (−0.1, 0)
Specificity	1/8 (12.5%)	0/8 (0%)	12.5% (0.1, 2.0)
Accuracy	21/29 (72.4%)	23/31 (74.2%)	1.8% (0.1, 2.0)
PEM poststudy			
Sensitivity	20/21 (95.2%)	23/23 (100%)	4.8% (0, 2.0)
Specificity	4/8 (50.0%)	1/8 (12.5%)	37.5% (0.2, 2.0)
Accuracy	24/29 (82.8%)	24/31 (77.4%)	5.4% (−0.1, 0.3)
Surgery prestudy			
Sensitivity	19/21 (90.5%)	19/23 (82.6%)	7.9% (−0.1, 0.3)
Specificity	4/8 (50.0%)	2/8 (25.0%)	25.0% (−0.2, 0.7)
Accuracy	23/29 (79.3%)	21/31 (67.7%)	11.6% (0.1, 2.0)
Surgery poststudy			
Sensitivity	18/21 (85.7%)	20/23 (87.0%)	1.3% (−0.2, 2.0)
Specificity	6/8 (75.0%)	2/8 (25%)	50.0% (0.2, 2.0)
Accuracy	24/29 (82.8%)	22/31 (71.0%)	11.8% (0.1, 2.0)

sics for acute abdominal pain did not report any significant adverse events.[3–6] Given our sample size, we were unable to adequately evaluate significant adverse events. A recent study of adult patients hinted at higher adverse outcome rates in patients who received unspecified analgesic agent for acute abdomen. But the authors could not demonstrate a causal relationship between analgesia and increased rate of adverse outcome due to multiple confounding factors.[14] A multicenter trial with a very large sample size is required to truly evaluate the adverse outcomes of patients who receive opioid analgesia for their abdominal pain.

The need for analgesia in patients with acute abdominal pain is based on a variety of factors: severity of the pain, need for diagnostic testing, availability of consultants, and the treating physician's comfort with diagnosis or analgesic use. Our findings suggest that the use of intravenous opioids in children with moderate to severe acute abdominal pain is possible without the fear of significant changes in physical findings or delay in diagnosis. However, extrapolation of our findings to younger children must be cautioned, due to their inherent difference in causes of abdominal pain and difficulty in assessment.

Limitations and Future Questions

A limitation to our study is that the same physician performed the pre- and poststudy medication examination in which the knowledge of the prestudy medication assessment may have biased the poststudy medication diagnosis. That is to say, the treating emergency physician will always have initial physical examination findings, and will use that information in the subsequent evaluation of the patient. In a real-life case scenario, the consulting surgeon may examine the patient after analgesia given by the emergency physician. In this situation, the consulting surgeon has to make a clinical decision based on the post-morphine evaluation only. We did not evaluate the impact of single examination after the analgesia. A second limitation is the lack of experience in the surgical consultants (residents), in spite of which, their diagnostic accuracy was very similar to that of the PEM physicians. This limitation may actually strengthen our findings since it is likely that a more experienced surgeon would have even more accurate diagnostic skills. Our intention was to enroll patients in a consecutive manner. We could not control for each treating physician's view of clinical need for vascular access and/or surgical consultation. Thus, the third limitation may be a selection bias, as we could not differentiate those enrolled from the all the potentially eligible patients who were seen in the ED. The last limitation is the small sample size with inadequate power to achieve significant difference in the diagnostic accuracy between the groups.

Two distinct strengths of our study are enrollment of only those patients meeting our highly selective criteria (resulting in a more homogeneous patient population that clinically needed analgesia), and concurrent evaluation by ED staff and surgical consultants for all enrolled patients.

The future direction in studying analgesia for abdominal pain lies in multicenter trials that have adequate power to show significant improvement in diagnostic accuracy. In addition, degree of satisfaction, subjective comfort level achieved from different doses of various opioid analgesics, adverse events, long-term outcomes, and these effects in younger children need to be addressed. A trial of analgesia before surgical evaluation looking at the resultant diagnostic accuracy is also needed.

Conclusions

We found that intravenous morphine provides significant pain reduction to selected children with moderate to severe abdominal pain without adversely affecting the abdominal examination. Furthermore, intravenous morphine did not affect the diagnostic accuracy in identifying surgical conditions in children with acute abdominal pain.

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APPENDIX A

List of Diagnoses Provided on the Data Entry Form

Acute appendicitis (perforated)
Acute appendicitis (non-perforated)
Acute gastroenteritis
Bowel obstruction
Constipation
Mesenteric adenitis
Nonspecific abdominal pain
Ovarian disease
Peptic ulcer disease
Pelvic inflammatory disease

Erratum

An author's degree was listed incorrectly in the following article in the February 2002 issue of *Academic Emergency Medicine*: Beckman AW, Sloan BK, Moore GP, et al. Should Parents Be Present during Emergency Department Procedures on Children, and Who Should Make That Decision? A Survey of Emergency Physician and Nurse Attitudes. Acad Emerg Med. 2002; 9:154–8. Mitchell J. Goldman is listed as having an MD degree; the correct degree is DO.