Efficacy and Impact of Intravenous Morphine Before Surgical Consultation in Children With Right Lower Quadrant Pain Suggestive of Appendicitis: A Randomized Controlled Trial

Benoit Bailey, MD, MSc
Sylvie Bergeron, MD
Jocelyn Gravel, MD, MSc
Jean-François Bussières,
    BPharm, MSc, MBA
Arie Bensoussan, MD

From the Division of Emergency Medicine (Bailey, Bergeron, Gravel), the Division of Clinical Pharmacology and Toxicology (Bailey), Department of Pediatrics (Bailey, Bergeron, Gravel), the Department of Pharmacy (Bussières), and the Department of Surgery (Bensoussan), CHU Sainte-Justine, Montreal, Quebec, Canada.

Study objective: The evidence supporting the use of analgesia in children with abdominal pain suggestive of appendicitis is limited. The objectives of the study are to evaluate the efficacy of morphine before surgical consultation in children presenting to the pediatric emergency department (ED) with right lower quadrant pain suggestive of appendicitis and determine whether it has an impact on the time between arrival in the ED and the surgical decision.

Methods: All children between the ages of 8 and 18 years who presented to a pediatric ED with a presumptive diagnosis of appendicitis were eligible to be enrolled in a randomized double-blind placebo-controlled trial if the initial pain was at least 5 of 10 on a verbal numeric scale. Patients received either 0.1 mg/kg of intravenous morphine (maximum 5 mg) or placebo. The primary outcomes were (1) the difference in pain using a visual analog scale at baseline and 30 minutes after the completion of the intervention, analyzed by comparing the mean pain differences for the treatment versus placebo groups; and (2) the time between arrival in the ED and the surgical decision, analyzed by comparing the median delay for the 2 groups.

Results: Ninety patients with a suspected diagnosis of appendicitis were randomized to receive morphine or placebo. Both groups were similar in terms of demographics, medical history, physical findings, emergency physician assessment of the probability of appendicitis, and initial pain score. There was no important difference in the decrease of pain between the morphine (n=45) and placebo (n=42) groups 30 minutes after the intervention: 24±23 mm and 20±18 mm, respectively (Δ 4 mm [95% confidence interval [CI] −5 to 12 mm]). There was also no important difference in the time between arrival in the ED and the surgical decision: median 269 minutes (95% CI 240 to 355 minutes) for morphine and 307 minutes (95% CI 239 to 415 minutes) for placebo (Δ −34 minutes [95% CI −105 to 40 minutes]).

Conclusion: The use of morphine in children with a presumptive diagnosis of appendicitis did not delay the surgical decision. In our group of patients, however, morphine at a dose of 0.1 mg/kg was not more effective than placebo in diminishing their pain at 30 minutes. [Ann Emerg Med. 2007;50:371-378.]

INTRODUCTION

The fear of masking a surgical condition, such as appendicitis, has traditionally justified withholding analgesia in patients presenting with acute abdominal pain. Delayed diagnosis and treatment of appendicitis are associated with an increased rate of perforation, resulting in increased rates of morbidity and mortality.[1,2] This reasoning has been the cornerstone of the dogma that "it is really prudent to withhold morphine until a reasonable diagnosis has been made and a plan of action formulated."[3,4] There is, however, no study to support this assumption.

Editor's Capsule Summary

What is already known on this topic

Although many studies have demonstrated that opioids do not interfere with the diagnosis of acute abdomen, early analgesia is not yet routine practice, particularly for children.

What question this study addressed

In 8- to 18-year-old children with moderate to severe right-lower-quadrant abdominal pain, does morphine (0.1 mg/kg intravenously) delay the surgical disposition decision?

What this study adds to our knowledge

In this 90-person randomized trial, intravenous morphine did not delay surgical decisionmaking, a particularly compelling finding, given the high prevalence of appendicitis in the sample (66%). Placebo effect was unusually strong in this study, resulting in pain relief similar to that of morphine.

How this might change clinical practice

This study provides persuasive evidence that physicians should routinely provide analgesia to children with possible appendicitis.

Research we'd like to see

Now that it seems well established that lower doses of opioids are safe in acute abdominal pain, it appears justified to study analgesic titration to a greater degree of pain relief.

The evidence supporting the use of analgesia in adults with abdominal pain is growing, and it appears that analgesia does not impair diagnostic clinical accuracy.[5] For children, there are still a limited number of small studies to support this, although no study contradicts this premise.[6-8] In spite of these studies, resistance to analgesia use in children with acute abdominal pain is still present.[9,10]

The objectives of the study were to evaluate the efficacy of morphine before surgical consultation in children presenting to the pediatric emergency department (ED) with right lower quadrant pain suggestive of appendicitis and determine whether it had an impact on the time between arrival in the ED and the surgical decision. Time to surgical disposition was used as a surrogate outcome because it has been demonstrated that the rate of adverse effects is positively correlated with the delay in surgery.[1,2,11,12]

MATERIALS AND METHODS
Study Design

We conducted a randomized double-blind placebo-controlled trial from February 2004 to June 2006 of children presenting to a pediatric ED with acute right lower quadrant abdominal pain suggestive of appendicitis. The institutional review board approved the study. Written informed consent

was obtained from either parent, as well as written or verbal assent for all children.

Setting and Selection of Participants

Patient enrollment took place in the ED at a tertiary care urban pediatric center with an annual census of more than 60,000 visits. All children between the ages of 8 and 18 years who presented to the ED with right lower quadrant abdominal pain and a presumptive diagnosis of appendicitis requiring a surgical consultation were eligible regardless of the time of day. The specific inclusion criteria were age between 8 and 18 years, right lower quadrant abdominal pain of 3 days or fewer, verbal numeric pain score of at least 5 of 10 (0 is no pain and 10 the worst pain), presumptive diagnosis of appendicitis, and the need for surgical consultation. A presumptive diagnosis of appendicitis meant that the patient had to present at least 2 of the following signs or symptoms: migration of pain (from periumbilical to right lower quadrant), vomiting, oral temperature greater than 38°C (100.4°F), right lower quadrant tenderness, right lower quadrant guarding, indirect tenderness (Rovsing's sign), or psoas sign.[13-17] The exclusion criteria were appendicitis proven by ultrasonography or computed tomography (CT) before surgical assessment, analgesia other than acetaminophen or ibuprofen given before enrollment, hemodynamically unstable, sepsis, immunocompromised, and all patients with a history of sickle cell anemia, abdominal surgery, inflammatory bowel disease, pancreatic or biliary disease, allergy to morphine, and suspected or present pregnancy.

All patients presenting to the ED with abdominal pain were evaluated for potential participation in the study. Those who met the inclusion criteria and for whom no exclusion criteria existed were approached to participate in the study by one of the pediatric emergency physicians working full time in the ED. After written informed consent and assent were obtained, the study protocol was started.

First, patients graded their pain on a 100-mm visual analog scale. They were not reminded of their previous response when asked verbally to rate their pain to assess eligibility in the study; this last number was also not recorded by the emergency physician. The anamnesis and physical examination were performed by the treating physician with a standardized form. This same physician graded the probability of appendicitis on a 100-mm visual analog scale.

The patient then received the intervention of interest: either morphine at 1 mg/mL or a similar-looking placebo (both vials contained the same amount of a clear liquid). The study nurse chose the next available numbered bottle containing either morphine or placebo.

Investigations, including laboratory tests, plain abdominal radiograph, and abdominal ultrasonography, were ordered according to the treating physician's choice. A second evaluation of the patient was performed by the same emergency physician 30 minutes after the completion of the medication infusion; the physician was blinded to the laboratory, radiograph, and

ultrasonographic results. Pain assessment was performed with the visual analog scale. The physician evaluated the patient by using the same standardized form. He or she graded the probability of appendicitis on the 100-mm visual analog scale as before. Then, the physician tried to guess the treatment allocation.

The surgical consultant, either the attending physician or senior resident, was asked to assess the patient within 2 hours after receipt of the study medication and after the 30-minute assessment made by the emergency physician. We chose this period to be certain that morphine had attained its peak effect (after 30 minutes) and that the effect was still present at the assessment by the surgical consultant (before 120 minutes). They proceeded as usual and ordered other complementary tests, including laboratory tests, ultrasonography, or CT, as they deemed necessary before finishing with the patient. Disposition included either discharge or scheduling for laparotomy or laparoscopy. If patients were admitted for observation, the disposition occurred when the patient was scheduled for laparotomy or laparoscopy or was discharged from surgery care.

Any physician was able to administer additional analgesic after the patient was assessed by the surgical consultant.

Interventions

Patients were randomized to receive either 0.1 mg/kg of morphine (maximum 5 mg) or a similar-looking placebo intravenously during 20 minutes.

Computer-generated block randomization with blocks of variable size was done. The randomization list was drawn up by the statistician and given directly to the pharmacy department. Independent pharmacists dispensed either morphine or normal saline solution in a similar-looking solution. The medication was available in the ED at all times in a locked cabinet. At the end of the study, the code was revealed to the researchers once data collection was completed for all patients.

All personnel (nurses, physicians, surgeons, and pathologists) and patients and parents were blinded to the treatment assignment until study completion. To evaluate the blinding, emergency physicians were asked to guess the treatment allocated at the moment of the second evaluation.

Outcome Measures

There were 2 primary outcomes: (1) the difference in pain with the visual analog scale at baseline and 30 minutes after the completion of the intervention, and (2) the time between arrival at the ED and the time of the surgery consultant decision for the disposition of the patient (planning of laparotomy or laparoscopy or discharge from surgery care).

The secondary outcomes measured were proportion of perforated appendicitis, proportion of unnecessary laparotomy or laparoscopy, proportion of missed diagnoses, proportion of admission for observation, duration of hospital course, effect of the intervention on the probability of appendicitis as a diagnosis, effect of the intervention on the physical examination

(rebound tenderness and involuntary guarding), and any adverse effects caused by the intervention.

Pain assessment was performed using a visual analog scale. The difference in the visual analog scale at baseline and 30 minutes after the intervention was recorded in the standardized form.

Time to surgical disposition was defined as the time between arrival at the ED and the time of the surgery consultant decision for the disposition of the patient (planning of laparotomy or laparoscopy or discharge from surgery care).

The proportion of perforated appendicitis was evaluated with surgical procedure description and the histologic diagnosis recorded in the patient's medical record. In case of discrepancy, pathologic results had a higher importance than surgical procedure record.

The proportion of unnecessary laparotomy was evaluated with surgical procedure description and the histologic diagnosis recorded in the patient's medical record. In case of discrepancy, pathologic results had a higher importance than the surgical procedure record. The laparotomy was defined as unnecessary if the pathologic findings failed to fulfill criteria mandating a surgical approach (appendicitis, ovarian torsion, etc).

The proportion of missed diagnoses was evaluated for all patients hospitalized for appendicitis after enrollment into the study but previously discharged from the ED.

The proportion of admission for observation was evaluated from the medical record.

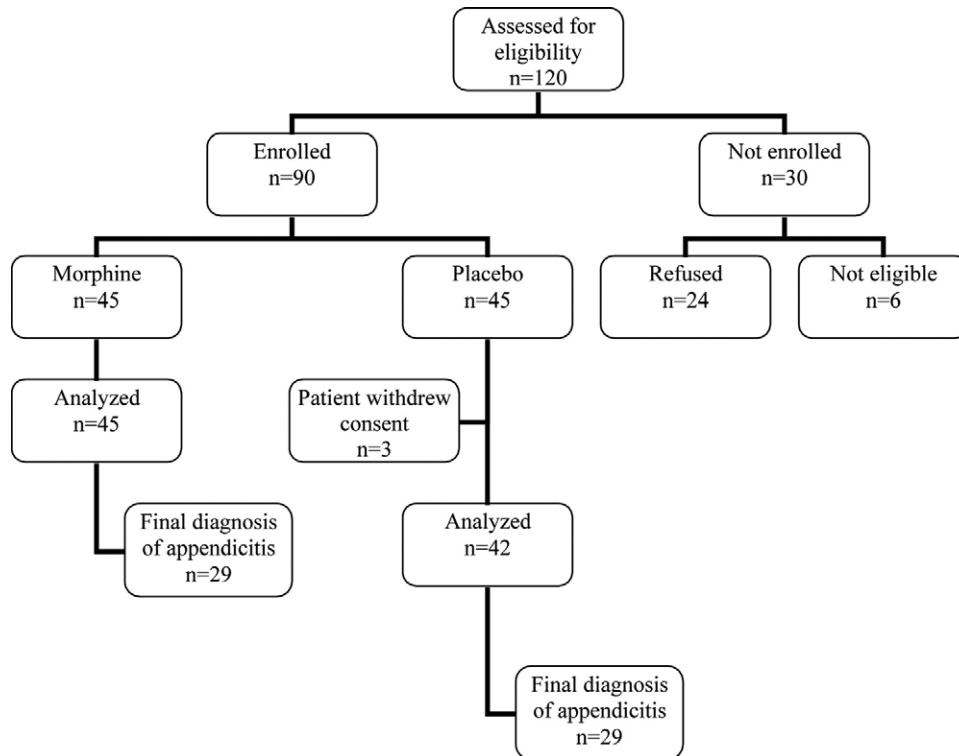The duration of hospitalization was evaluated from the medical record.

The effect of the intervention on the probability of appendicitis as a diagnosis was evaluated with a visual analog scale. The same attending physician graded the probability of appendicitis with a 100-mm visual analog scale (0 is a diagnosis of appendicitis impossible; 100 is a certain diagnosis of appendicitis) at baseline and 30 minutes after the completion of the intervention. The surgical consultant, either the attending physician or senior resident, did the same evaluation after the intervention.

The proportion of change in the presence of rebound tenderness and involuntary guarding pre- and postintervention was evaluated with the standardized form.

Nurses and physicians were instructed to look for morphine adverse effects such as decreased level of consciousness, presence of pruritus, or a rash.

Data Collection and Processing

Data were collected prospectively on a standardized form. Exceptions included the following: proportions of perforated appendicitis, unnecessary laparotomy, missed diagnoses, admission for observation, and duration of hospitalization. For these outcomes, medical record review was performed by the principal investigator of all patients enrolled in the study by using a second standardized form. Definitions used were described previously. The reviewer was blinded to the study

Figure 1. Study flowchart.

group at the record review; there was no attempt to measure interrater reliability.

Primary Data Analysis

The sample size was calculated for the 2 primary outcomes. The mean value of visual analog scale change in previous studies of analgesia in abdominal pain in children was 20 mm, with an SD of 25.[6] It was also previously reported that a difference of 13 mm in the visual analog scale was the minimal clinically significant difference for pain.[18] Using an α value of .05, a power of 90%, and a formula provided to calculate sample size for the difference between 2 means,[19] we calculated that the minimal needed number of patients should be 76 patients per arm. Because of the expected skewed distribution for time to surgical disposition, the nonparametric method of Chebychev was used to calculate the sample size.[20] The minimum difference found clinically significant was targeted at 1 hour by consensus of our full-time pediatric emergency physicians, with an expected SD of 3 hours. Because of this, 92 patients had to be recruited per arm.

Because of slow enrollment, once 90 patients were recruited, we decided to perform an interim analysis of the results to determine whether the study should continue. One of the investigators analyzed the data by an a priori method. Because the delay was lower in the morphine group compared with the placebo by 34 minutes, we thought it was unlikely that another 90 patients would have a 90-minute difference in favor of the placebo group.

Data were analyzed with SPSS (version 13.0; SPSS Inc., Chicago, IL). The 95% confidence interval (CI) of the median was calculated with CIA (version 2.1.2; Southampton, UK).

Patients were analyzed with an intention-to-treat approach.

A Student's *t* test or Mann-Whitney test whenever appropriate was performed to compare mean or median visual analog scale change and mean or median time to surgical disposition in the 2 intervention groups. A *P* value of .05 was defined as statistically significant.
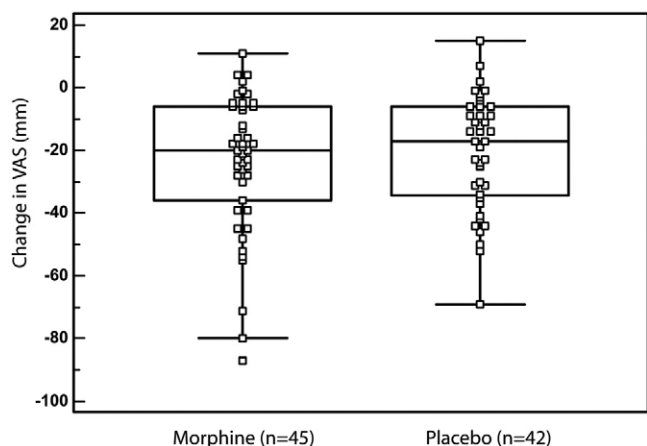
RESULTS

A total of 120 children were assessed for eligibility and 90 children were randomized (Figure 1). Of the 45 patients randomized to receive the placebo, 3 patients withdrew after receiving the intervention but before the 30-minute assessment because of parental doubt about the potential effect of morphine in their child. All 45 patients randomized to receive the morphine were available for analysis of the primary outcome. Both groups were similar in terms of demographics, medical history, physical findings, probability of appendicitis, and initial pain scores (Table 1). Nineteen physicians enrolled patients in the study.

The median dose of morphine administered was 4 mg (interquartile range 3.2, 4.9 mg) There was no difference in the decrease of pain after morphine and placebo administration: 24±23 mm and 20±18 mm, respectively (Δ 4 mm [95% CI −5 to 12 mm]) (Figure 2). There was also no difference in the

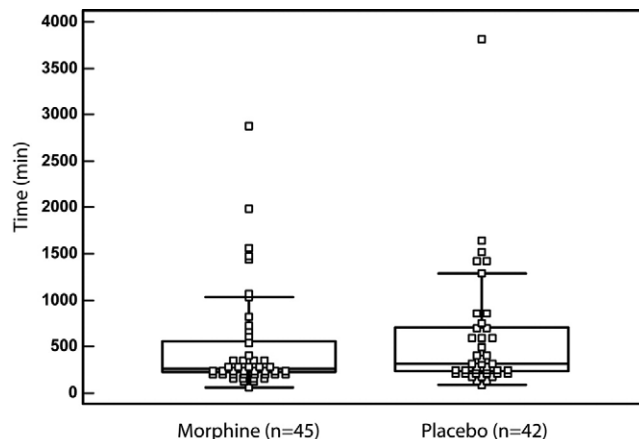**Table 1.** Characteristics of the patients enrolled in the study.

Characteristics	Morphine	Placebo
Age, mo*	11.3±2.2	11.2±2.5
Boys	30 (67)	28 (66)
Duration of pain, h	24±18	31±23
Fever at home	10 (22)	10 (24)
Anorexia	34 (76)	36 (86)
Vomiting	28 (63)	29 (69)
Diarrhea	7 (15)	11 (27)
Migration of pain	22 (49)	19 (45)
Temperature at triage (°C)	37.2±0.9	37.2±0.8
Involuntary guarding	34 (76)	30 (71)
Rebound tenderness	38 (84)	35 (83)
McBurney sign	44 (98)	42 (100)
Obturator sign	17 (37)	12 (28)
Psoas sign	22 (49)	20 (48)
Rovsing's sign	22 (49)	62 (26)
Suspicion of peritonitis	17 (37)	14 (33)
Probability of appendicitis (mm)	78±13	77±17
Initial pain score, mm	67±19	67±17

*Data are presented as either No. (%) or mean±SD unless otherwise indicated.

Figure 3. Difference in time between arrival in ED and surgical decision in the placebo and the morphine groups.

Table 2. Results of secondary outcome for the morphine group (n=45) and the placebo group (n=42).

Outcome	Morphine, No. (%)	Placebo, No. (%)
Had laparoscopy or laparotomy	33 (73)	32 (76)
Pathological diagnosis of appendicitis	29/33 (88)	29/32 (91)
Perforated appendicitis	6/29 (21)	8/29 (28)
Normal laparoscopy or laparotomy	3/33 (9)	2/32 (6)
Missed diagnosis	0	1 (2)
Admitted for observation	5 (11)	5 (12)
Median duration of hospitalization and IQR, days	2 (1.5–4.4)	2 (1–3.5)
Lost involuntary guarding after the intervention	7/31 (23)	6/26 (33)
Lost rebound tenderness after the intervention	10/35 (29)	4/30 (13)
Adverse effect of the intervention	4 (9)	0

Figure 2. Change in visual analog scale after the intervention in the placebo and the morphine groups.

decrease between the morphine and the placebo group, which is expressed in percentage according to the initial pain level: 33%±32% versus 32%±28%, respectively (Δ 1% [95% CI −12% to 14%]).

There was no difference between the time of arrival to the ED and the time of surgical decision (operating room or discharge) in the 2 groups (Δ −34 minutes [95% CI −105 to 40 minutes]): median of 269 minutes (95% CI 240 to 355 minutes) for morphine and 307 minutes (95% CI 239 to 415 minutes) for placebo (Figure 3). Also, there was no difference between the start of the intervention and the time of surgical decision in the 2 groups (Δ 10 minutes [95% CI −48 to 60 minutes]): median of 165 minutes (95% CI 96 to 255 minutes) in the morphine group versus 156 minutes (95% CI 115 to 249 minutes) in the placebo group. Furthermore, there was no difference between the time of arrival to the ED and the time of entry into the operating room for the subgroup of patients who

had surgery (Δ 16 minutes [95% CI −162 to 1,135 minutes]): median of 513 minutes (95% CI 377 to 653 minutes) for morphine (n=35) and median of 498 minutes (95% CI 351 to 760 minutes) for placebo (n=32).

The proportion of perforated appendicitis, unnecessary laparotomy or laparoscopy, missed diagnosis, admission for observation, adverse effect of intervention, and the duration of hospital course in the 2 groups is presented in Table 2.

In the placebo group, diagnosis in patients who had surgery included appendicitis (n=29), normal appendix (n=2), and ovarian torsion (n=1). Other diagnoses in that group were mesenteric adenitis (n=1), abdominal abscess (n=1), ovarian cyst (n=1), and abdominal pain (n=7). In the morphine group, the diagnosis in patients who had surgery included appendicitis (n=29), normal appendix (n=3), ovarian cyst (n=2), and perforated Meckel diverticulum (n=1). Other diagnoses in the morphine group were ovarian cyst (n=1), pyelonephritis (n=1), and abdominal pain (n=8).

The only missed diagnosis was in the placebo group. The patient was treated 9 days after being discharged from the ED

for a recurrence of abdominal pain. He was asymptomatic for 7 days between the ED visits and was found to have an abdominal abscess.

Four patients who received morphine had adverse effects, 1 patient each for itching, vomiting, change in level of consciousness (drowsiness), and nausea with dizziness.

The intervention had no effect on the probability of appendicitis as a diagnosis assessed by the emergency physicians. The median change in the probability of appendicitis between the pre- and the postintervention as assessed by the emergency physician in the morphine group was 0 mm (95% CI −3 to 3 mm), and in the placebo group, it was 0 mm (95% CI −3 to 3 mm). The median change in the probability of appendicitis between the postintervention assessment by the emergency physician and the surgical consultant in the morphine group was 12.5 mm (95% CI −1 to 25 mm), and in the placebo group, it was 7 mm (95% CI −5 to 28 mm).

Ultrasonography was performed in 15 (33%) patients in the morphine group (including 7 of the 15 girls) and in 16 (38%) patients in the placebo group (including 9 of the 15 girls). No CT scans were done, as is customary in our center.

In total, the proportion of patients who lost involuntary guarding or rebound tenderness was no different between the morphine and placebo groups (Table 2). In the group without appendicitis, a subanalysis showed that 7 of 11 (64%) patients who received morphine compared with 0 of 6 (0%) who received placebo lost rebound tenderness: Δ 64% (95% CI 15% to 85%). For the patients with appendicitis, there was no difference in the loss of rebound tenderness, 3 of 24 (12%) and 4 of 23 (17%) for morphine and placebo, respectively: Δ −5% (95% CI −26% to 16%). With regard to involuntary guarding, there was no difference between those with or without appendicitis.

In the morphine group, the emergency physicians' perception that the patient had received morphine was accurate in 26 of 45 (58%) cases, whereas in the placebo group, their perception that the patient had received placebo was accurate in 21 of 42 (50%) cases: Δ 8% (95% CI −13% to 27%).

LIMITATIONS

Limitations of the study include the fact that morphine was no better than placebo to decrease the pain. We can speculate that the absence of difference in clinical accuracy as measured by various surrogate outcomes was caused by the absence of difference in the pain reduction between the morphine and the placebo groups. However, both interventions decreased the pain by more than what is found to be clinically significant, 13 mm.[18] We stopped the trial after 50% of the initial estimate of the required sample size. The difference between the 2 groups was so small that it was unlikely to have become significant even with twice the number of patients, considering the large effect of the placebo. The use of a surrogate outcome such as time to surgical disposition may be debatable. However, a study using perforated appendicitis or other adverse events as the primary outcome would need a huge sample size.[12] Furthermore, lack of

effect on time to surgical disposition may have been caused by the number of physician involved (emergency physicians and surgery consultants). We have addressed one of the limitations of previous studies mentioned by Ranji et al[5]: diagnosis certainty (probability of appendicitis as a diagnosis) was evaluated before and after the intervention by the emergency physicians and also by the surgical consultant after the intervention.

We chose a maximum dose of 5 mg of morphine. A total of 11 (24%) patients of 45 who received morphine received the maximum dose. Had we chosen a higher maximum dose, 10 mg for example, we could have had different results. However, this is unlikely because response was similar in patients who did receive the maximum dose and those who did not receive this maximum: 30±19 mm versus 21±23 mm, respectively (Δ 8 mm; 95% CI −7 to 24 mm).

Also, we chose to enroll children aged 8 to 18 years to facilitate visual analog scale administration. Thus, conclusion from this study can be applied only to children aged 8 to 18. Because our center has some unique features, including the use of ultrasonography to assist in the diagnosis and not CT scan and treats French- and English-speaking patients, we do not know how well the results can be generalized to other centers.

DISCUSSION

The results from this randomized double-blind placebo-controlled trial confirm that the use of opiates in children with abdominal pain suggesting appendicitis does not impair the ability of the surgeon to make a decision. Opiates can modify the physical examination, as demonstrated by the loss of rebound tenderness in patients without appendicitis. However, in our study, morphine was not more effective than placebo in decreasing the pain. This result adds to the evidence supporting the use of analgesia in children with acute abdominal pain. In one randomized controlled trial of 60 children treated in a pediatric ED that included 23 (38%) patients with appendicitis, intravenous morphine (0.1 mg/kg) was associated with a significant reduction in pain (median 2/10 cm [95% CI 1 to 4 cm]) compared with the placebo group while making no difference in the number of patients undergoing laparotomy, in the evaluation time from triage to laparotomy, and in diagnostic accuracies.[6] In patients with surgical conditions, the use of morphine did not alter the presence of tenderness.[6] In another randomized controlled trial of 63 children with undifferentiated acute abdominal pain treated by a surgeon, including 21 (33%) patients with appendicitis, oral oxycodone (0.1 mg/kg, the equivalent of an intravenous morphine dose of 0.1 mg/kg) was associated with a significant reduction in pain (mean 13/100 mm [95% CI 2 to 24 mm)] compared with the placebo group and did not affect the diagnostic accuracy.[7] Finally, in a third randomized controlled trial of 108 children who required a surgical consultation in a pediatric ED, including 57 (53%) patients with appendicitis, intravenous morphine (0.05 mg/kg) was associated with a significant reduction in pain (mean 1/10 cm; *P*=.015) compared with the placebo group and did not

affect confidence in the diagnosis on a 0% to 100% scale (Δ 1.2% [95% CI −2.9% to 5.3%] and Δ 0.01% [95% CI −0.39% to 0.40%] for the emergency physician and the surgeon, respectively).[8]

In our trial, the decrease of rebound tenderness in patients without appendicitis caused by morphine did not appear to impair the final diagnosis and may have helped to rule out an acute abdomen. However, although we have also shown that morphine did not alter the clinical accuracy as measured by the time to surgical disposition or by the proportion of perforated appendicitis, unnecessary laparotomy or laparoscopy, missed diagnosis, admission for observation, and the effect of the intervention on the probability of appendicitis as a diagnosis, we did not find that morphine caused a significant reduction in pain compared to the placebo. The majority of the adult studies have shown a decrease in pain after opiate administration; some did not.[5] All pediatric studies have shown opiates to be effective in reducing the pain.[6-8] This was not the case in our trial, although morphine did reduce pain by a mean of 24 mm. In our trial, a majority (66%) of patients had a diagnosis of appendicitis compared to 33% to 53% in the other studies. This difference also does not explain our finding, because pain reduction was similar in the morphine and the placebo group even when we compared patients with a diagnosis of appendicitis and those without a diagnosis of appendicitis.

Our reduction in pain with morphine, as assessed by a visual analog scale, was similar to that of the other studies: 24 mm compared to 21 to 40 mm in other pediatric studies.[6-8] Thus, the difference must lie in the placebo response, which was high in our study: 20 mm compared to 9 to 11 mm in other pediatric studies.[6-8] The reason for this is unclear, considering that the characteristics of the patients were similar in both groups. The explanation of the study by the emergency physicians could have increased the placebo response by suggesting to the children that we were expecting a decrease in pain after the intervention.[21] There is no method to verify this a posteriori. High placebo effect in adolescents is not surprising.[22,23]

This trial adds to the existing evidence that analgesia in children with acute abdominal pain, and in particular those with appendicitis, does not appear to impair diagnostic accuracy. In the future, a large multicenter study should evaluate adverse events such as perforated appendicitis.

Address for correspondence: Benoit Bailey, MD, MSc, FRCPC, CHU Ste-Justine, 3175 Chemin de la Côte-Ste-Catherine, Montréal, Quebec, Canada H3T 1C5; 514-345-4931 ext 6276, fax 514-345-4823; E-mail benoit.bailey@umontreal.ca.

REFERENCES

1. Maxwell JM, Ragland JJ. Appendicitis: improvement in diagnosis and treatment. *Am Surg*. 1991;57:282-285.
2. Von Titte SN, McCabe CJ, Ottinger LW. Delayed appendectomy for appendicitis: causes and consequences. *Am J Emerg Med*. 1996; 14:620-622.
3. Silen W. *Cope's Early Diagnosis of the Acute Abdomen*. New York, NY: Oxford University Press; 1987.
4. American College of Emergency Physicians. Clinical policy: critical issues for the initial evaluation and management of patients presenting with a chief complaints of nontraumatic acute abdominal pain. *Ann Emerg Med*. 2000;36:406-415.
5. Ranji S, Goldman L, Simel D, et al. Do opiates affect the clinical evaluation of patients with acute abdominal pain? *JAMA*. 2006; 296:1764-1774.
6. Kim MK, Strait RT, Sato TT, et al. A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med*. 2002;9:281-287.
7. Kokki H, Lintula H, Vanamo K, et al. Oxycodone versus placebo in children with undifferentiated pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. *Arch Pediatr Adolesc Med*. 2005;159:320-325.
8. Green R, Bullock B, Kabani A, et al. Early analgesia for children with acute abdominal pain. *Pediatrics*. 2005;116:978-983.
9. Vane D. Efficacy and concerns regarding early analgesia in children with acute abdominal pain. *Pediatrics*. 2005;116:1018.
10. Goldman R, Crum D, Bromberg R, et al. Analgesia administration for acute abdominal pain in the pediatric emergency department. *Pediatr Emerg Care*. 2006;22:18-21.
11. Graff L, Radford MJ, Werne C. Probability of appendicitis before and after observation. *Ann Emerg Med*. 1991;20:503-507.
12. Lee JS, Stiell IG, Wells GA, et al. Adverse outcomes and opioid analgesic administration in acute abdominal pain. *Acad Emerg Med*. 2000;7:980-987.
13. Mahadevan M, Graff L. Prospective randomized study of analgesic use for ED patients with right lower quadrant abdominal pain. *Am J Emerg Med*. 2000;18:753-756.
14. Paulson EK, Kalady MF, Pappas TN. Suspected appendicitis. *N Engl J Med*. 2003;348:236-242.
15. Golledge J, Toms AP, Franklin IJ, et al. Assessment of peritonism in appendicitis. *Ann R Coll Surg Engl*. 1996;78:11-14.

16. Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med.* 1986;15:557-564.

17. Izbicki JR, Knoefel WT, Wilker DK, et al. Accurate diagnosis of acute appendicitis: a retrospective and prospective analysis of 686 patients. *Eur J Surg.* 1992;158:227-231.

18. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med.* 1996;27: 485-489.

19. Armitage P, Berry G. *Statistical Methods in Medical Research.* Oxford, England: Blackwell Scientific Publications; 1994.

20. Riffenburgh RH. *Statistics in Medicine.* San Diego, CA: Academic Press; 1999.

21. Goodenough B, Kampel L, Champion G, et al. An investigation of the placebo effect and age-related factors in the report of needle pain from venipuncture in children. *Pain.* 1997;72:383-391.

22. Turner J, Deyo RA, Loeser J, et al. The importance of placebo effects in pain treatment and research. *JAMA.* 1994;271:1609-1614.

23. Simeon J, Wiggins D. The placebo problem in child and adolescent psychiatry. *Acta Paedopsychiatr.* 1993;56:119-122.

Did you know?

You can save your online searches and get the results by e-mail.

Visit www.annemergmed.com today to see what else is new online!