Effect of pain control in suspected acute appendicitis on the diagnostic accuracy of surgical residents

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ABSTRACT

Objective: To determine the influence of early pain relief for patients with suspected appendicitis on the diagnostic performance of surgical residents.

Methods: A prospective randomized, double-blind, placebo-controlled trial was conducted for patients with suspected appendicitis. The patients were randomized to receive placebo (normal saline intravenous [IV]) infusions over 5 minutes or the study drug (morphine 5 mg IV). All of the clinical evaluations by surgical residents were performed 30 minutes after administration of the study drug or placebo. After obtaining the clinical probability of appendicitis, as determined by the surgical residents, abdominal computed tomography was performed. The primary objective was to compare the influence of IV morphine on the ability of surgical residents to diagnose appendicitis.

Results: A total of 213 patients with suspected appendicitis were enrolled. Of these patients, 107 patients received morphine, and 106 patients received placebo saline. The negative appendectomy percentages in each group were similar (3.8% in the placebo group and 3.2% in the pain control group, $p = 0.62$). The perforation rates in each group were also similar (18.9% in the placebo group and 14.3% in the pain control group, $p = 0.75$). Receiver operating characteristic analysis revealed that the overall diagnostic accuracy in each group was similar (the area under the curve of the placebo group and the pain control group was 0.63 v. 0.61, respectively, $p = 0.81$).

Conclusions: Early pain control in patients with suspected appendicitis does not affect the diagnostic performance of surgical residents.

RÉSUMÉ

Objectif: L'étude visait à déterminer l'incidence du soulagement précoce de la douleur chez des patients souffrant vraisemblablement d'appendicite, sur l'efficacité de la pose du diagnostic par les résidents en chirurgie.

Méthode: Un essai comparatif contre placébo, prospectif, à répartition aléatoire et à double insu a été mené chez des patients souffrant vraisemblablement d'appendicite. Ceux-ci ont reçu au hasard soit un placébo (solution physiologique salée intraveineuse [i.v.]) en 5 minutes, soit le médicament à l'étude (morphine, 5 mg, i.v.). Toutes les évaluations cliniques ont été réalisées par les résidents en chirurgie, 30 minutes après l'administration du placébo ou du médicament à l'étude. Après confirmation des probabilités cliniques d'appendicite par les résidents en chirurgie, un examen par tomodensitométrie abdominale a été effectué. L'objectif principal était de comparer l'incidence de l'administration de la morphine, par voie intraveineuse, sur la capacité des résidents en chirurgie à poser le diagnostic d'appendicite.

Résultats: Au total, 213 patients souffrant vraisemblablement d'appendicite ont participé à l'étude. Sur ce nombre, 107 ont reçu de la morphine, et 106, la solution salée placébo. Le pourcentage d'appendicectomie négative était comparable dans chaque groupe (3.8% dans le groupe placébo et 3.2% dans le groupe de soulagement de la douleur; $p = 0.62$). Le taux de perforation était également comparable dans chacun des groupes (18.9% dans le groupe placébo et 14.3% dans le groupe de soulagement de la douleur; $p = 0.75$). L'analyse caractéristique de la performance d'un test a révélé que, dans l'ensemble, l'exactitude diagnostique était comparable dans chaque groupe (la surface sous la courbe dans le groupe placébo et celle dans le groupe de soulagement de la douleur étaient de 0.63 et de 0.61, respectivement; $p = 0.81$).

Conclusion: Le soulagement précoce de la douleur chez les patients souffrant vraisemblablement d'appendicite n'a pas d'incidence sur la pose du diagnostic par les résidents en chirurgie.

Keywords: acute appendicitis, emergency department, morphine

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Acute appendicitis is one of the most common conditions requiring surgery in emergency department (ED) patients.[1] Diagnosis is made from the physical examination, the patient history, and diagnostic imaging. Pain relief was traditionally delayed for fear that it may affect the physical examination and prevent an accurate diagnosis. The administration of analgesics for patients with unspecified abdominal pain has been an area of disagreement between surgeons and emergency physicians in the past.[2] More recently, studies have demonstrated the safety of analgesics for abdominal pain, showing that early pain control reduces the stress response and may even improve the physical examination.[3–7] However, there were limitations to those studies, including a small sample size,[4,5,7] a lack of double-blinded methods,[6] and diagnoses that were conducted primarily by emergency physicians.[3,4] To overcome these limitations, a larger double-blind study comparing the diagnostic performance of surgery residents was conducted herein to evaluate the effect of pain control in patients with suspected appendicitis.

METHODS

Study design and setting

We conducted a prospective, randomized, double-blind, placebo-controlled trial for patients with suspected acute appendicitis from October 2007 to May 2009 at an urban, tertiary care emergency department (ED) with an annual admittance of 65,000 patients. The Institutional Review Board of our hospital approved this study, and all participants gave valid informed consent.

Study subjects

This study enrolled patients who visited the ED with suspected acute appendicitis.[8] All nonpregnant patients $>$ 15 years old who presented with nontraumatic right lower quadrant pain of less than 48 hours' duration were eligible for the study. Patients who were transferred from other hospitals with a diagnosis of appendicitis or were given analgesics for abdominal pain were excluded. Patients with renal insufficiency or allergy to computed tomography (CT) contrast dye were excluded from the study.

Study protocol and data acquisition

All patients were initially examined by an emergency physician, which included emergency residents and specialists in emergency medicine (Figure 1), and if the patient appeared to be eligible, the research nurse (H.M.P.) was notified. The research nurse confirmed the study criteria and obtained informed consent. After consent was obtained, the research nurse used a visual analogue scale (VAS) to determine the patient's subjective level of pain. Then the patients were randomized to receive placebo (normal saline intravenous [IV]) or study drug (morphine 5 mg IV). Randomization was performed by the treating nurse using a random number generator in a 1:1 ratio using permuted random block sizes of 4, 6, and 8. Sequentially numbered, opaque, and sealed envelopes were prepared by the research nurse and used by the treating nurse. All personnel (emergency physicians, surgical residents, and research nurses) involved in the study were blinded to the assignment. Thirty minutes after the administration of analgesics, the patient's VAS score was measured by the research nurse.

First- to fourth-year surgical residents participated in this study. All of the clinical evaluations were performed by surgical residents 30 minutes after the administration of the placebo or the study drug. The surgical residents were asked to predict the probability that the patients had acute appendicitis by choosing one of four groups corresponding to clinical probabilities of 80 to 100%, 60 to 79%, 40 to 59%, and 20 to 39%.[9,10]

After obtaining the clinical probability of acute appendicitis, abdominal CT scans (Brilliance, Phillips Medical Systems, Cleveland, OH) were performed. Contrast material (Ultravist 370, Schering, Berlin, Germany) was infused at a dose of 2 mL/kg. The disposition (discharge or operation and admission) of the patient was determined by a surgical resident after considering the physical examination, patient history, laboratory tests, and CT results. Standardized data collection forms were used throughout the study, including demographic information, patient symptoms and signs, and laboratory test results.

Objectives

The primary objective was to compare the diagnostic performance of surgical residents for patients who received or did not receive analgesics. The final diagnosis of acute appendicitis was based on pathology

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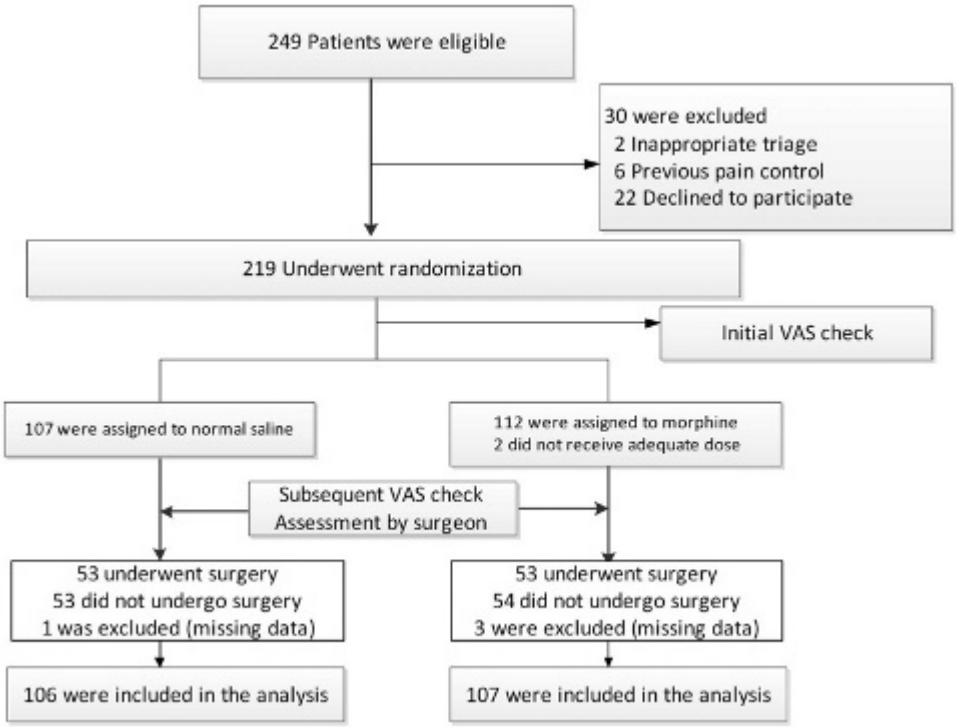

Figure 1. Study scheme. VAS = visual analogue scale.

after the operation. In cases where no operation was performed, a clinical follow-up or a telephone interview was conducted after 3 months. The secondary objectives included a negative appendectomy rate, a perforation rate, and the VAS score before and after medication.

Data analysis

For the sample size calculation, we used data from our previous study regarding the diagnostic performance of surgical residents.[10] The area under the curve (AUC) of surgical residents was 0.66, and we assumed that pain control could mask the diagnosis of appendicitis up to an AUC of 0.5. To obtain 90% statistical power with a one-sided α equal to 0.05, it was necessary to have 106 patients in each group. Assuming a dropout rate of 10%, 117 patients per group were required. Paired *t*-tests were used to compute differences in VAS scores between the two groups. We performed receiver operating characteristic (ROC) curve analysis to compare the diagnostic accuracy of the surgical residents. The AUC was calculated and compared.

Statistical analyses were conducted using *STATA* software version 10.0 (StataCorp, College Station, TX).

RESULTS

A total of 249 patients with abdominal pain suggestive of appendicitis were enrolled. Of these patients, 36 patients were excluded. The reasons for exclusion were 1) patient refusal to participate in the study (n = 22); 2) previous medication for pain control (n = 6); 3) insufficient dose of medication (n = 2); 4) inappropriate triage (n = 2); and 5) missing data (n = 4). A total of 107 patients received analgesics, and 106 patients did not receive analgesics (Figure 2).

A total of 213 patients were included in the final study. The mean age was 37.3 ± 0.1 years; 105 patients (46.9%) were male, and 118 patients (53.1%) were female. The most common additional symptoms were nausea (43%), anorexia (38%), and vomiting (19%) (Table 1). In the pain control group, there was a significant difference in VAS scores 30 minutes after the administration of morphine, but there was no change in VAS scores in the no pain control group 30 minutes after the administration of saline (Table 2). A total of 116 patients received an appendectomy; 4 of these patients did not have acute appendicitis. The overall negative appendectomy rate was 3.4%, and the appendiceal perforation rate was 16.4% (Table 3). The test characteristics of the surgical residents' diagnoses

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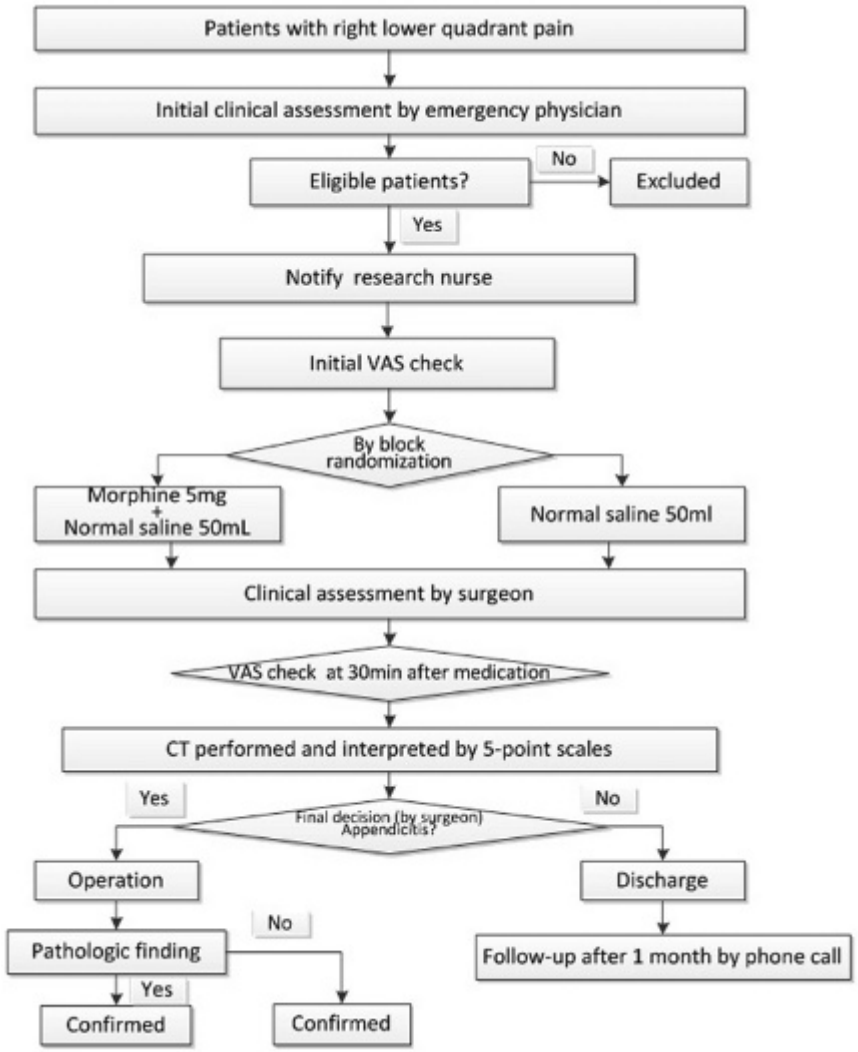

Figure 2. Study flow diagram. CT = computed tomography; VAS = visual analogue scale.

are shown in Table 4. The clinical probabilities of acute appendicitis predicted by the surgical residents for patients receiving morphine or the placebo are presented in Figure 3. There was no significant difference in the probabilities of acute appendicitis predicted by surgical residents for patients who received morphine compared to those who did not. The ROC analysis revealed that the overall diagnostic accuracy in each category did not differ between the morphine group and the placebo group ($p = 0.81$) (Figure 4).

DISCUSSION

In this prospective, randomized, controlled study, the diagnostic performance of surgical residents for acute appendicitis in patients with abdominal pain suggestive of appendicitis did not differ significantly between the morphine group and the placebo group. To the best of our knowledge, this is the first report to compare surgical resident diagnostic performance between patients with suspected appendicitis receiving morphine versus placebo.

Acute abdominal pain is one of the most common presenting symptoms in the ED.[11,12] Historically, it was recommended that no analgesics be administered for fear of obscuring the diagnosis.[2,13,14] Recent studies investigating early analgesic administration for abdominal pain have suggested that this practice does not reduce diagnostic accuracy. These studies have some limitations, such as limited or obscured involvement of surgeons, follow-up performed by on-study physicians, inadequate pain control, and a small sample size.[15] Based on these studies, some have concluded that analgesia prior to diagnosis and disposition should be given only after the consent of the surgeon.[2,16,17]

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Table 1. Baseline characteristics (*N* = 213)

	No pain control (106)	Pain control (107)
Age	36.4 ± 1.4	38.2 ± 1.4
Sex, *n* (%)		
Male	44 (41.5)	56 (52.3)
Female	62 (58.5)	51 (47.7)
Symptoms and signs, *n* (%)		
Anorexia	43 (40.6)	39 (36.4)
Nausea	46 (43.4)	46 (43.0)
Vomiting	23 (21.7)	18 (16.8)
Temperature	36.8 ± 0.7	36.8 ± 0.6
Temperature > 37.3°C (9.1°F)	38.3 ± 0.8	37.8 ± 0.5
Temperature > 38.0°C (100.4°F)	38.8 ± 0.6	39.0 ± 1.3
White blood cell count (μL)	11632.9 ± 4348.4	11008.9 ± 4433.3
White blood cell count > 10,000/μL	14337.0 ± 3270.3	13692.66 ± 3559.2
Segmented neutrophils (%)	74.2 ± 10.6	75.2 ± 12.9
Segmented neutrophils > 75%	82.5 ± 5.0	82.9 ± 4.6
C-reactive protein (CRP)	4.21 ± 5.3	4.8 ± 5.7
Hospitalization period (d)	3.98 ± 2.1	4.02 ± 2.7

There were no significant differences between groups, other than a slightly higher mean temperature in the placebo group. For temperatures above 38°C, there was no significant difference ($p = 0.61$).

Moreover, some recent surveys have revealed that surgeons remain reluctant to provide early analgesia without a definitive diagnosis.[18]

Previous studies enrolled all patients with acute abdominal pain, which caused some debate about the recommended sample size of future studies. In one study, only 7% of patients with acute abdominal pain were ultimately diagnosed with a condition that, if missed, might result in increased mortality or morbidity.[19] Due to this low incidence, the investigators recommended that at least 1,500 patients be included to obtain significant differences in adverse outcomes between pain control and no pain control groups. To date, no study has included such large numbers of

Table 2. Results of VAS scores, surgical residents' assessment, and CT results

	Placebo	Morphine	*p*
Initial VAS	6.75 ± 2.14	6.50 ± 1.09	
After 30 min VAS	6.50 ± 2.47 ($p = 0.19$)	4.38 ± 2.56 ($p = 0.02$)	
SR assessment			
n (%)	Total = 106	Total = 107	0.76
80–100	25 (23.6)	28 (26.2)	
60–79	38 (35.9)	39 (36.5)	
40–59	28 (26.4)	22 (20.6)	
20–39	15(14.2)	18 (16.8)	
CT results			
n (%)	Total = 103	Total = 105	0.45
Definitely not	53 (51.5)	50 (47.6)	
Probably not	3 (2.9)	2 (1.9)	
Indeterminate	3 (2.9)	0 (0.0)	
Probably	6 (5.8)	5 (4.8)	
Definitely	38 (36.9)	48 (45.7)	

CT = computed tomography; SR = surgical residents; VAS = visual analogue scale.
CT results for grade 3 (indeterminate) or higher was defined as acute appendicitis.

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Table 3. Results of appendectomy

Results	No pain control, *n* (%)	Pain control, *n* (%)	Total, *n* (%)	*p* value
Operation	53	63	116	0.10
No appendicitis	2 (3.8)	2 (3.2)	4 (3.4)	0.62
Perforated appendicitis	10 (18.9)	9 (14.3)	19 (16.4)	0.75

Four patients showed no pathologic evidence of appendicitis. The two patients in the no pain control group and one patient in the pain control group had only serosal congestion. The remaining one patient in pain control group had appendiceal tumor.

Table 4. Diagnostic sensitivity, specificity, and likelihood ratio (diagnostic performance level set to 3, 95% CI)

	Pain control, % (95% CI)	No pain control, % (95% CI)
Sensitivity	73.0 (60.1–83.1)	67.9 (53.6–79.7)
Specificity	52.3 (36.9–67.3)	49.1 (41.0–66.4)
Positive likelihood ratio	1.53 (1.08–2.16)	1.33 (1.07–2.04)
Negative likelihood ratio	0.52 (0.31–0.85)	0.65 (0.38–0.94)

patients; in actuality, the total number of patients in all published articles is below this level. In the present study, we focused on patients with suspected appendicitis to determine the difference in diagnostic performance of surgical residents in the presence or absence of pain control in patients. This design is more appropriate to ascertain the impact of pain control for abdominal pain from suspected appendicitis. In patients presenting to the ED with abdominal pain, the priority is to determine the need for surgery, and appendicitis is the most common disease requiring surgery that presents in the ED.[20] Furthermore, the diagnosis of appendicitis is evident by pathology or clinical follow-up. The diagnosis for patients with general abdominal pain is occasionally obscure; and in one study of pain control, the main diagnosis was abdominal pain itself.[7]

Previously, we studied the diagnostic performance of surgical residents' clinical impressions.[9] In this study, the AUC of the surgical residents' clinical impressions was the same as in our previous data, supporting minimal bias. Previous studies of children have attempted to determine whether pain control impeded the diagnosis of appendicitis, but these studies relied on the surgeon's own confidence in diagnosis and did not use a real diagnostic standard.[4,21]

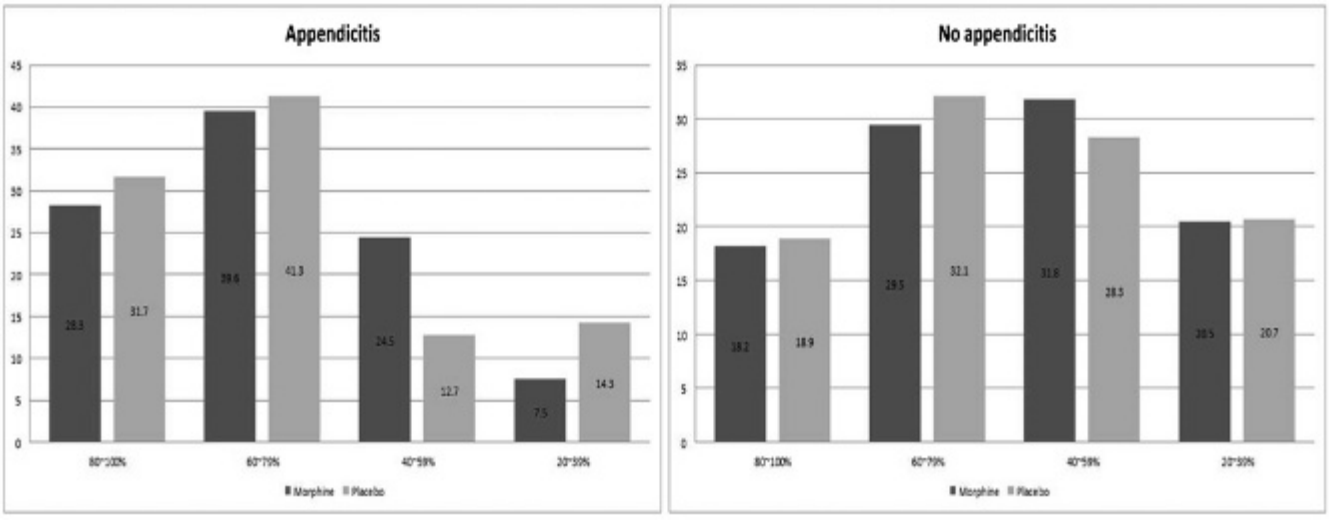

Figure 3. Clinical probability of appendicitis determined by surgical residents in both patient groups.

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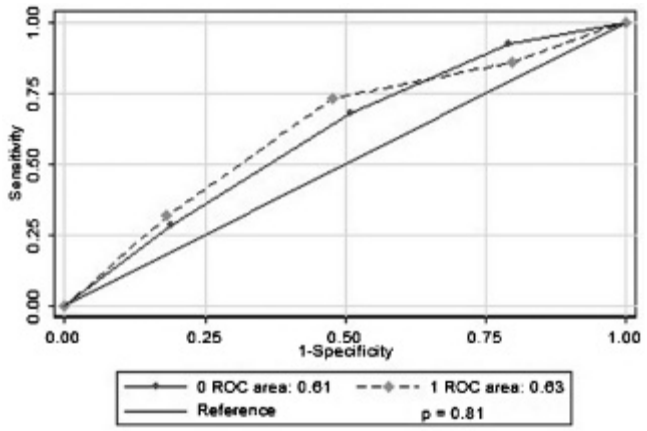

Figure 4. Compared receiver operating characteristic (ROC) curves of clinical probability. The area under the curve of the no pain control group and the pain control group is 0.61 (95% CI 0.50–0.71) and 0.63 (95% CI 0.52–0.73), respectively, $p = 0.81$.

We obtained an opinion from the surgical service only after pain control. Some studies investigated changes in physical examination or clinical impression before and after pain control as a primary objective, but this design may cause some informational bias.

Theoretically, and as suggested by some studies, pain control may alter the findings of physical examinations and may have an effect on the patient's disposition, especially when patients are given high amounts of analgesics.[3,6,18,22] However, this study showed that the overall clinical impression was similar with or without pain control. The administration of analgesics did not appear to affect the patient's disposition. Moreover, standard practice for abdominal pain in the ED is changing, and CT scans are increasingly used in the diagnosis of abdominal pain in the ED.[23] A recent study reported that performing CT altered the leading diagnosis in approximately 50% of cases.[24] In this randomized controlled trial, the administration of pain medication did not significantly reduce the diagnostic performance of surgical trainees for suspected appendicitis.

In this study, the appendiceal perforation rates and negative appendectomy rates were comparable in both groups, indicating that both the sensitivity and the specificity of the entire diagnostic process were independent of the morphine administration.

LIMITATIONS

This study has several limitations. First, this study was conducted at one institution and may not be generalized to other institutions. Second, the surgical clinical opinion in this study was provided by surgical residents, and the results may differ when board-certified surgeons are used. Third, the administration of pain control was not based on the patient's weight; however, the distribution of weight was comparable between the two groups.

CONCLUSION

The diagnostic performance of surgical residents in predicting suspected appendicitis did not differ significantly between patients given IV morphine analgesia and those given placebo. Our results support the practice of early pain control with morphine in ED patients suspected of having acute appendicitis.

Competing interests: None declared.

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