Comparative Effectiveness of Patient-Controlled Analgesia for Treating Acute Pain in the Emergency Department

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Study objective: We assess the effectiveness of patient-controlled analgesia in the emergency department (ED). We hypothesized that decline in pain intensity from 30 to 120 minutes after initial intravenous opioid administration is greater in patients receiving morphine by patient-controlled analgesia compared with usual care and would differ by a clinically significant amount.

Method: This was a pragmatic randomized controlled trial of patient-controlled analgesia and usual care (opioid and dose at physician’s discretion) in 4 EDs. Entry criteria included age 18 to 65 years and acute pain requiring intravenous opioids. The primary outcome was decline in numeric rating scale pain score 30 to 120 minutes postbaseline. Secondary outcomes included satisfaction, time to analgesia, adverse events, and patient-controlled analgesia pump-related problems. We used a mixed-effects linear model to compare rate of decline in pain (slope) between groups. A clinically significant difference between groups was defined as a difference in slopes equivalent to 1.3 numeric rating scale units.

Results: Six hundred thirty-six patients were enrolled. The rate of decline in pain from 30 to 120 minutes was greater for patients receiving patient-controlled analgesia than usual care (difference = 1.0 numeric rating scale unit; 95% confidence interval [CI] 0.6 to 1.5; P < .001) but did not reach the threshold for clinical significance. More patients receiving patient-controlled analgesia were satisfied with pain management (difference = 9.3%; 95% CI 3.3% to 15.1%). Median time to initial analgesia was 15 minutes longer for patient-controlled analgesia than usual care (95% CI 11.4 to 18.6 minutes). There were 7 adverse events in the patient-controlled analgesia group and 1 in the usual care group (difference = 2.0%; 95% CI 0.04% to 3.9%), and 11 pump-programming errors.

Conclusion: The findings of this study do not favor patient-controlled analgesia over usual ED care for acute pain management. [Ann Emerg Med. 2017; -:1-10.]

Please see page XX for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background

Analgesics were prescribed at approximately 97 million ED visits in the United States in 2011.1 Titration of analgesia to pain relief, coupled with frequently repeated pain assessment, is generally regarded to be the optimal method of pain control.2 However, this process is time consuming and not always feasible in crowded emergency departments (EDs).3

Use of patient-controlled analgesia may be a more feasible alternative to clinician-driven titration and redosing. Patient-controlled analgesia enables patients to self-administer small intravenous boluses of an analgesic at predetermined doses and frequency. It has the potential to address interindividual variation in analgesic need, as well as features of the ED environment that compromise individualized attention to pain management.3

Patient-controlled analgesia is used extensively in postoperative care. A Cochrane review of 49 randomized controlled trials of patient-controlled analgesia versus conventional administration found that pain control and satisfaction were higher in the patient-controlled analgesia groups.4 Published data on ED patient-controlled analgesia usage are limited. Two small studies found no differences when substituting patient-controlled analgesia for time-intensive nurse titration of intravenous opioids (1-mg to 2-mg morphine boluses until adequate pain relief). Authors of both studies concluded that patient-controlled...
Editor’s Capsule Summary

What is already known on this topic
Patient-controlled analgesic opioid dosing is useful in hospital to optimize relief and safety.

What question this study addressed
Would an emergency department (ED)-based patient-controlled analgesia approach improve perceived pain relief compared with usual care?

What this study adds to our knowledge
In a 636-subject randomized study in 4 urban EDs, the rate of numeric pain decline did not differ between patient-controlled analgesia and usual care approaches, with longer time needed to initial analgesia and more frequent adverse events observed with patient-controlled analgesia.

How this is relevant to clinical practice
Widespread ED patient-controlled analgesia use will not improve care.

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analgesia is as effective as individual titration of intravenous morphine by a nurse and may be used in place of it. However, individual titration by clinical staff is unlikely to constitute usual ED care.

The authors of 2 recently conducted randomized trials comparing patient-controlled analgesia with routine care of ED patients found significantly less pain during a 12-hour period in patients with abdominal pain treated with patient-controlled analgesia but not in those with pain from trauma.

We previously conducted a randomized trial of patient-controlled analgesia in ED patients with abdominal pain. Patients in the patient-controlled analgesia group received a loading dose of intravenous morphine of 0.1 mg/kg followed by demand dosing of 1.0 or 1.5 mg morphine, with a 6-minute lockout period. Patients in the comparison group received the same weight-based morphine loading dose followed by physician-initiated additional dosing. We found no difference in the first 30 minutes and a clinically and statistically significant greater decline in pain (1.5 numeric rating scale units) from 30 to 120 minutes in patients treated with patient-controlled analgesia. More patients receiving patient-controlled analgesia were satisfied with their pain treatment. There were no differences in the incidence of side effects or adverse events. This previous study, designed to evaluate ED patient-controlled analgesia efficacy and safety, was limited to patients with abdominal pain at a single ED site, used a standardized loading dose for all groups, and employed a dedicated research nurse to administer analgesia and monitor patients.

The present study assesses the generalizability of the previous findings to more naturalistic conditions, with patient-controlled analgesia initiated and monitored by ED nurses, initial intravenous analgesic and dose of the comparison group at the discretion of the treating physician, application to a broader sample of ED patients, and multiple ED sites with different equipment, volume, staffing, and training.

Importance
If ED patient-controlled analgesia use is demonstrated to be more effective than usual care, it will significantly add to available ED pain management options.

Goals of This Investigation
The primary goal was to compare the effectiveness of a specified patient-controlled analgesia regimen to usual opioid analgesia care provided in the ED. We hypothesized that the rate of decline in pain scores from 30 to 120 minutes would differ between groups and that the difference would be clinically significant. A value of 1.3 numeric rating scale units has been used as a standard definition of a clinically significant difference between treatment groups. We sought to assess the generalizability of findings across clinical sites and for different locations of pain. An additional goal was to assess secondary measures of effectiveness, safety, and side effects.

MATERIALS AND METHODS
Study Design and Setting
This was a multicenter randomized controlled trial of patient-controlled analgesia versus usual care. The study was approved by the institutional review board of Albert Einstein College of Medicine. Data were collected from April 30, 2013, through February 25, 2016.

Initial ED study sites were Jacobi Medical Center, Bronx, NY (municipal hospital with 75,000 annual adult ED visits), Moses Division of Montefiore Medical Center, Bronx, NY (108,000 annual adult ED visits), and Hospital of the University of Pennsylvania, Philadelphia, PA (57,000 annual ED visits). We discontinued data collection at the Hospital of the University of Pennsylvania because of slow enrollment and added the Weiler Division of Montefiore Medical Center, Bronx, NY (71,000 annual ED visits).
Selection of Participants

Patients aged 18 to 65 years whose emergency physician planned to administer intravenous opioid analgesics and was amenable to using patient-controlled analgesia were eligible for inclusion during hours when research associates were available. Research associate coverage varied by site, ranging from 8 AM to midnight on weekdays to 24 hours, 7 days per week, depending on supplementary site-specific resources. Consecutive patients were screened during these times. Patients were excluded if they required resuscitation; had long-term use of opioids (daily for more than 1 week within the past year or methadone ever); had opioid use in past 24 hours, chronic pain syndromes, clinician suspicion of current or past opioid dependence or abuse, or altered mental status or intoxication; were expected to require procedural sedation; were pregnant or breast feeding; had a history of chronic obstructive pulmonary disease or sleep apnea; had baseline oxygen saturation (room air) less than 97%; had systolic blood pressure less than 100 mm Hg; received specific medications (benzodiazepines, monoamine oxidase inhibitors, phenothiazines, or tricyclic antidepressants); had a history of renal insufficiency or failure; had morphine allergy; were unable to provide informed consent or understand or operate a patient-controlled analgesia device; or had previous study entry. Research associates identified potentially eligible patients at triage through contact with nurses and surveillance of the electronic whiteboard. Once the physician determined that the patient would receive intravenous opioids, the research associate described the study and oral consent was obtained from the patient. Before initial treatment (baseline) and at triage through contact with nurses and surveillance of the electronic whiteboard, the research associates asked patients about nausea, vomiting, and respiratory rate at baseline and every 15 minutes thereafter up to 120 minutes. Every 30 minutes, the research associates asked patients to rate their pain intensity on a verbally administered numeric rating scale, ranging from 0 (“no pain”) to 10 (“worst possible pain”). This scale has been shown to be valid and reliable for assessment of acute pain in the ED.11 Research associates measured oxygen saturation by pulse oximetry, blood pressure, pulse rate, and respiratory rate at baseline and every 15 minutes thereafter up to 120 minutes. Every 30 minutes, the research associates asked patients about nausea, vomiting, and pruritus and observed the level of sedation by using a modified Ramsay Sedation Scale.12 At the end of the study, the research associates asked patients to rate their satisfaction with pain management, preference for the same treatment in the future for similar pain, and desire for additional analgesics. The latter was reported to clinical staff. Pain and sedation scores recorded for study purposes were not shared with nurses or providers.

Interventions

The intervention for the patient-controlled analgesia group consisted of a loading dose of intravenous morphine at 0.1 mg/kg, demand dose of intravenous morphine at 1 mg, lock-out interval (time from the end of delivery of one dose until the device was able to respond to another demand for analgesia) of 6 minutes, and physician-managed analgesic supplementation as needed. Patient-controlled analgesia was paused if patients left the ED for any reason, such as imaging tests. The usual care group received an intravenous opioid and dose chosen by the ED attending physician. Physician-managed analgesic supplementation was ordered as needed, with all medications administered by the ED nurse. The patient-controlled analgesia pump used at Jacobi Medical Center was the PainSmart IOD (Information on Demand) ambulatory infusion system (Moog Medical Devices Group, Elma, NY). Montefiore sites used the Hospira Gemstar infusion system (Hospira Inc., San Jose, CA). The Hospital of the University of Pennsylvania used the Hospira LifeCare patient-controlled analgesia infusion system (Hospira Inc.).

Patient-controlled analgesia was not in routine use in the Jacobi Medical Center ED at the start of the study. Thus, the hospital pain management nurse trained several trainers, who then conducted structured sessions with ED nurses in patient-controlled analgesia use. Patient-controlled analgesia was already in use for sickle cell patients at the Montefiore EDs and treatment of trauma patients at the Hospital of the University of Pennsylvania. Nursing staff at these sites had previously received patient-controlled analgesia competency training at their hiring. Nurses at these sites received information about the study but did not undergo additional training.

Methods of Measurement

After randomization, the research associates collected age, sex, weight, location and duration of pain, and use of analgesics before ED presentation from the ED record, physician, or patient. Before initial treatment (baseline) and at 30, 60, 90, and 120 minutes postbaseline, the research associates asked patients to rate their pain intensity on a verbally administered numeric rating scale, ranging from 0 (“no pain”) to 10 (“worst possible pain”). This scale has been shown to be valid and reliable for assessment of acute pain in the ED.11 Research associates measured oxygen saturation by pulse oximetry, blood pressure, pulse rate, and respiratory rate at baseline and every 15 minutes thereafter up to 120 minutes. Every 30 minutes, the research associates asked patients about nausea, vomiting, and pruritus and observed the level of sedation by using a modified Ramsay Sedation Scale.12 At the end of the study, the research associates asked patients to rate their satisfaction with pain management, preference for the same treatment in the future for similar pain, and desire for additional analgesics. The latter was reported to clinical staff. Pain and sedation scores recorded for study purposes were not shared with nurses or providers. Nurses performed
pain and sedation assessments according to nursing protocol and used them as they would in usual practice. Vital sign measurements obtained by the research associates that met criteria for adverse events were reported immediately to clinical staff. The research associates collected information about drug, dose, and time of physician-initiated administration of analgesics from the electronic medical record. The dose of hydromorphone, the only intravenous opioid administered other than morphine, was converted to morphine equivalent units (1 mg hydromorphone = 7 mg morphine). The research associates prospectively recorded any occurrences of oxygen supplementation or ventilatory assistance, fluid administration or vasopressors for hypotension, and administration of naloxone. Information about time and dosing of morphine dispensed on the patient-controlled analgesia pump was recorded automatically and electronically retrieved from the pump.

Patient-controlled analgesia pump malfunctions were observed and documented by the research associates. Patient-controlled analgesia operator error was determined by systematic review of all pump output after a research associate brought an operator error to the investigators’ attention.

Outcome Measures

The primary outcome was difference between treatment groups in rate of decline in pain (defined as slope of the regression line) from 30 to 120 minutes after the initial opioid dose. Secondary outcomes included patient satisfaction with pain management, preference for the same treatment in the future for similar pain, and desire for additional analgesics at 120 minutes. Time to initial analgesic administration was calculated as time of first opioid administration minus time when the research associate ascertained the patient met basic inclusion criteria. Side effects were incidence of nausea, vomiting, and pruritus, and level of sedation. The safety outcomes were incidence of adverse events (defined as any of the following: oxygen supplementation or ventilatory assistance, fluid administration or vasopressors for hypotension, administration of naloxone, oxygen saturation less than 92% on room air, respiratory rate less than 10 breaths/min, systolic blood pressure less than 90 mm Hg), patient-controlled analgesia device malfunction, and patient-controlled analgesia operator error.

Primary Data Analysis

Characteristics of the sample are reported as mean and SD, median and interquartile range, or proportions, as appropriate. The primary statistical analysis was a mixed-effects linear model used to examine the difference between the rate of decline per hour of numeric rating scale pain scores from 30 to 120 minutes by treatment group. Fixed effects in the analysis included treatment group and indicators of site and location of pain. Random intercepts and random slopes for time at the individual level were included, as well as the cross-level interaction between treatment group and time. We tested our principal hypothesis with a z test of the coefficient of the treatment group–by-time interaction term (details in Appendix E1, available online at http://www.annemergmed.com).

Two additional planned analyses were conducted to determine whether treatment effect differed by study site and location of pain (abdominal versus nonabdominal). These analyses were performed by incorporating the interaction terms of time and treatment group with study site and pain location. z tests were performed to test the difference between slopes of the numeric rating scale scores over time by study site and pain location. All models were fitted with maximum likelihood estimation. A nominal significance criterion of .05 was used for all analyses.

To assess whether between-group differences in rate of decline in pain met the threshold for clinical significance (1.3 numeric rating scale units), we converted the rates of decline per hour to reflect the 90-minute period from 30 to 120 minutes. These rates of decline were calculated by combining the applicable regression coefficients (time, group, and group-by-time interactions, as appropriate) and multiplying by 1.5 to change numeric rating scale units from per-hour units to units per 90 minutes.

Treatment group differences between the incidence of all secondary outcomes are presented with 95% confidence intervals (CIs).

Each patient was included in the analysis to the extent that data were present. We tested the robustness of the primary analysis by carrying out multiple sensitivity analyses with imputation of missing observations (details in Appendix E1, available online at http://www.annemergmed.com).

All analyses were performed as intention to treat. The sample size was designed to detect with high probability a difference between study groups that corresponded to a clinically significant difference in pain over time. A mean difference of 1.3 units on the numeric rating scale for pain is considered to be the minimal clinically significant difference between group pain scores. Because the period between 30 and 120 minutes is 1.5 hours, a difference between slopes of 0.87 per hour represented a difference of 1.3 numeric rating scale units during the 30- to 120-minute period. We carried out Monte Carlo simulations of our study design and analysis to estimate statistical power. To achieve 0.95 power to
detect a per-hour difference in slope of 0.87 numeric rating scale units at the .05 significance level, approximately 150 patients were needed in each treatment group. Because we were interested in whether the effect observed in the earlier study could be generalized to different study sites and location of pain, we conducted a series of simulations to identify a sample size with adequate power to test the interaction between treatment group, time, and study site, and between treatment group, time, and pain location. A sample size of 750 participants (250 at each site, 560 with abdominal pain, 190 with other locations of pain) provided 0.82 power to detect a difference if the pain-location-specific effects of patient-controlled analgesia versus usual care differed by 0.8 per hour. This provided power of 0.99 to detect a site-specific per-hour difference between groups of 0.8 numeric rating scale units.

RESULTS

Of the 4,691 patients screened, 655 (14.0%) were randomized (Figure 1) and 636 (13.6%) enrolled. Common reasons for ineligibility were recent use of oral opioids or other exclusionary medications, chronic pain condition, and

![Figure 1. Patient flow diagram. PCA, Patient-controlled analgesia; COPD, chronic obstructive pulmonary disease.](image-url)
pregnancy or breast feeding. Of the 4,036 patients not randomized, 267 (6.6%) were excluded because the attending physician did not think the patient “warranted patient-controlled analgesia” or “was a good candidate for patient-controlled analgesia.” Ninety-one patients (2%) were excluded because the physician planned to administer one small bolus of intravenous opioid only; 258 patients (6.0%) refused to participate. Common reasons were “don’t like research,” “don’t want to take morphine/afraid of addiction,” and “want pain medication immediately.” More patients receiving patient-controlled analgesia were missing data after intervention (25) than usual care (7). This was due primarily to the need to stop patient-controlled analgesia when they left the ED for imaging studies.

The sample was predominantly women and Hispanic (Table 1). Three-quarters had abdominal pain and most had severe pain (pain score >7). The treatment groups were well matched on background characteristics. Three hundred seventeen patients were enrolled at Jacobi Medical Center, 192 at Moses, 106 at Weiler, and 21 at Hospital of the University of Pennsylvania.

Table 2 shows the amount of intravenous opioid patients in the 2 groups received in morphine equivalent

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCA, N = 306</th>
<th>UC, N = 330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>180 (59)</td>
<td>202 (61.2)</td>
</tr>
<tr>
<td>Male</td>
<td>126 (41)</td>
<td>128 (38.8)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>179 (59)</td>
<td>205 (62)</td>
</tr>
<tr>
<td>Black</td>
<td>69 (23)</td>
<td>80 (24)</td>
</tr>
<tr>
<td>White</td>
<td>22 (7)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (12)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>39 (12)</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>82 (19)</td>
<td>82 (22)</td>
</tr>
<tr>
<td>Location of pain, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>239 (78)</td>
<td>254 (77)</td>
</tr>
<tr>
<td>Extremity</td>
<td>32 (11)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Back</td>
<td>25 (8)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Genitals</td>
<td>6 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Buttocks</td>
<td>1 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Rectum</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Initial NRS pain intensity score, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>6 (2)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>7</td>
<td>29 (10)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>8</td>
<td>47 (15)</td>
<td>59 (18)</td>
</tr>
<tr>
<td>9</td>
<td>57 (19)</td>
<td>56 (17)</td>
</tr>
<tr>
<td>10</td>
<td>167 (55)</td>
<td>169 (51)</td>
</tr>
<tr>
<td>Received nonopioid analgesics before arrival to ED, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>86 (28)</td>
<td>105 (32)</td>
</tr>
<tr>
<td>No</td>
<td>220 (72)</td>
<td>225 (68)</td>
</tr>
</tbody>
</table>

UC, Usual care; NRS, numeric rating scale.

<table>
<thead>
<tr>
<th>Opioid Analgesic</th>
<th>Dose PCA, N = 306</th>
<th>UC, N = 330</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose, mean (SD)</td>
<td>8.0 (1.4)</td>
<td>5.1 (2.0)</td>
<td>2.9 (2.6–3.2)</td>
</tr>
<tr>
<td>Additional dose in 30 min after initial dose, mean (SD)</td>
<td>0.8 (1.2)</td>
<td>0.1 (0.5)</td>
<td>0.8 (0.6–0.9)</td>
</tr>
<tr>
<td>Additional dose 30 to 120 min after initial dose, mean (SD)</td>
<td>3.2 (3.6)</td>
<td>1.0 (2.1)</td>
<td>2.2 (1.7–2.6)</td>
</tr>
<tr>
<td>Total dose, mean (SD)</td>
<td>12.0 (4.3)</td>
<td>6.1 (2.9)</td>
<td>5.9 (5.2–6.4)</td>
</tr>
</tbody>
</table>

*1 mg morphine=1 MEU; 1 mg hydromorphone=7 mg MEU.
decrease in pulse oximetry to 88%. Two additional patients with patient-controlled analgesia received supplemental oxygen for pulse oximetry readings of 91% and 93%, and one had patient-controlled analgesia halted for oxygen saturation of 88%. One patient in the usual care group had a transient reading of 88% on room air. All events resolved with the interventions noted within the 2-hour study period. No patient had a respiratory rate less than 10 breaths/min or required naloxone.

We identified 11 cases of errors in pump programming. In all but one, patients received unintended background infusions of 1 mg morphine per hour, resulting in an additional 2 mg of morphine during the 2-hour study period. The pump of one patient was erroneously programmed to deliver a background infusion of 7 mg morphine per hour. None of these patients experienced an adverse event. There were no subsequent programming errors after remediation by the nursing staff and changes made to the electronic patient-controlled analgesia order set to explicitly specify no background infusion.

**LIMITATIONS**

Blinding of the treatment group was not considered desirable or feasible in this study for several reasons. First, subjects’ experience with the modality of analgesia administration itself (patient-controlled analgesia versus usual care) could be accomplished only if patients were aware of treatment assignment. Second, blinding would require subjects in significant pain to receive sham dosing.
on a patient-controlled analgesia pump, which was thought to be unethical. Physician blinding would require decisions about additional analgesic administration to be made without knowledge of whether active drug was simultaneously available for self-administration.

We did not achieve the planned sample size of 750 patients because of slower-than-expected recruitment. Furthermore, the patients we enrolled were not evenly divided among the sites. Although we had more than adequate power to test the effectiveness of patient-controlled analgesia in the overall sample, the ability to detect a difference in effectiveness by pain location and site may have been limited by the reduced sample size.

We did not adjust the significance level to account for multiple statistical tests. Had we used a Bonferroni adjustment for the 3 planned analyses in the total sample, site, and location of pain, the inferences would have been unchanged.

Resources did not permit continuous research associate coverage. However, consecutive samples of patients were enrolled during the hours research staff was available.

The full benefit of patient-controlled analgesia may accrue during a longer period than observed during the 2-hour duration of the study. Although this duration might be expected to be adequate to capture the ability of patient-controlled analgesia to address interindividual variability in initial opioid requirement, it may not be long enough to capture the full benefit of access to redosing in response to the diminishing effect of initial analgesic dose over time.

**Table 4.** Secondary measures of effectiveness at 120 minutes postbaseline.

<table>
<thead>
<tr>
<th>Measures of Effectiveness</th>
<th>PCA, No. (%)</th>
<th>UC, No. (%)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction at 120 min, † satisfied</td>
<td>247/281 (87.9)</td>
<td>254/323 (78.6)</td>
<td>9.3 (3.3 to 15.1)</td>
</tr>
<tr>
<td>Prefer same treatment in future, ‡</td>
<td>252/279 (90.3)</td>
<td>266/322 (82.6)</td>
<td>7.7 (2.2 to 13.1)</td>
</tr>
<tr>
<td>Want more pain medication at 120 min, § yes</td>
<td>69/278 (24.8)</td>
<td>131/321 (40.8)</td>
<td>-16.0 (-23.3 to -8.5)</td>
</tr>
</tbody>
</table>

* † Satisfied or very satisfied vs very unsatisfied, unsatisfied, or neutral in response to the question “How satisfied are you with the result of your pain treatment overall?”
‡ In response to the question “If you were to come to the ED again with the same kind of pain, would you like the same pain management you had today?”
§ In response to the question “Do you want more pain medication?”

**DISCUSSION**

This randomized trial provides a pragmatic assessment of ED patient-controlled analgesia by evaluating effectiveness in a broad sample of ED patients with pain requiring intravenous opioid analgesia under actual clinical and staffing conditions at multiple clinical sites, using a clinically relevant intervention as a comparison. The overall between-group difference in change in pain between 30 and 120 minutes, 1.0 numeric rating scale unit, failed to meet the threshold set a priori for clinical significance despite that patients in the patient-controlled analgesia group received more opioid than those who received usual care. This leads to a different inference about ED patient-controlled analgesia effectiveness than did our previous one-site study of efficacy, in which we found a clinically significant difference of 1.5 numeric rating scale units in patients with abdominal pain.

We designed the study to assess whether the effect of treatment differed between study sites and pain locations. The interaction between site and treatment was not statistically significant. However, the estimate of treatment effect at the site of the previous study, 1.5 numeric rating scale units, met the threshold for clinical significance, whereas at the 2 other sites with sufficient numbers of patients to make precise estimates, it did not (0.3 and 0.8 numeric rating scale units). The variability of these estimates suggests there may be a heterogeneous effect of patient-controlled analgesia at different sites; however, our study did not have adequate power to make this conclusion because of the difficulty of securing the planned sample.

Neither of the point estimates of difference in decline in pain between treatment groups for patients with abdominal pain, 1.2 numeric rating scale units, and pain at other locations, 0.5 numeric rating scale units, met the criterion for clinical significance, and the interaction term was not statistically significant. Smith et al recently conducted a randomized trial comparing patient-controlled analgesia with routine care in ED patients with moderate to severe abdominal pain and pain from trauma. They found significantly less pain during a 12-hour period in patients with abdominal pain treated with patient-controlled
analgesia but not in patients with trauma. Their results suggest there may be differences in effect by type of pain, although the magnitude of effect is difficult to interpret because the authors reported effectiveness as the difference between area under the curve of pain measurements during 12 hours.

The modest patient-controlled analgesia effect in our study mirrors the results of postoperative studies. In a meta-analysis of studies of postoperative pain in the first 24 hours after surgery, McNicol et al found a mean difference of 9 mm less pain on a 100-mm visual analog scale in patients treated with patient-controlled analgesia.

The study of abdominal pain by Smith et al, like our own, documented greater patient satisfaction with patient-controlled analgesia than the comparison groups. The meta-analysis of studies of patients treated with patient-controlled analgesia postoperatively had similar results. The authors posited that this may have been due to greater autonomy over pain control and reduced fear of not obtaining sufficient analgesia.

Seven patients in the present study who received patient-controlled analgesia experienced adverse events (2.3%) versus 1 usual care patient (0.3%). Although these adverse events resolved with minimal or no intervention, their excess incidence is concerning. The meta-analysis of postoperative studies found the incidence of respiratory depression (composite measure including respiratory rate less than 10 breaths/min and oxygen saturation less than 90%) to be similar between patient-controlled analgesia and comparison groups, 2.3% versus 2.0%.

There were 11 instances in which a pump was erroneously programmed to give constant background infusions. Although no associated adverse events occurred, potential for harm from this type of error increases with time. Patient-controlled analgesia medication errors in postoperative studies have been documented, although rates of error are difficult to quantify. Published recommendations to maximize safety include simplification of pump interface, use of pump-stored protocols, use of standard medication concentration, ongoing staff training, patient education, and policy requiring a second caregiver to review pump programming.

In summary, in this pragmatic trial, the difference in effectiveness between patient-controlled analgesia and usual care rates of decline in pain from 30 to 120 minutes did not reach a threshold for clinical significance. This finding, together with the incidence of adverse events and pump-programming errors, does not favor patient-controlled analgesia over usual care for acute pain management in the ED.

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Author contributions: PEB and AJB conceived the study, designed the trial, and obtained research funding. AMM, AKC, AR, and SP supervised the conduct of the trial and data collection at each site. CS provided statistical advice and PEB analyzed the data. EJG provided consultation and guidance on study design and the ongoing functioning of the study. PEB drafted the manuscript, and all authors contributed substantially to its revision. PEB takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX E1

Details of the primary analysis

The primary analysis is based on a random-slopes linear model of NRS score. In this model, time is represented as 2 variables, early (baseline to 30 minutes) and late (30 to 120 minutes), which constitute a linear spline with knot at 30 minutes, rescaled to hours rather than minutes.

Study arm is represented by a dichotomous variable, group, coded 1 for PCA and 0 for UC. Pain location is also dichotomous, abdominal=1, other location=0. The study site variable, site, is a 4-level variable coded 1=Moses, 2=Weiler, 3=JMC, or 4=Penn. This 4-level variable is in turn incorporated in the model as 3 dichotomous indicator variables, the reference category being Moses.

The model equations for the primary analysis are:

\[
NRS_{it} = b_0 + b_1 \text{group}_i + b_2 \text{Weiler}_i + b_3 \text{JMC}_i + b_4 \text{Penn}_i \\
+ b_5 \text{abdominal}_i + C_i \text{early}_i + D_i \text{late}_i + E_{\text{early-early}}_i \\
+ \text{group}_i + E_{\text{late-late}}_i + \text{group}_i + u_i + \epsilon_{it},
\]

\[
u \equiv N(0, \sigma^2) \text{ iid, } \epsilon \equiv N(0, \tau^2) \text{ iid, } u \text{ independent of } \epsilon.
\]

\[C_i = C + v_i; \ D_i = D + w_i; \ v \equiv N(0, \nu^2) \text{ iid, } w \equiv N(0, \varphi^2), \vphantom{N(0, \nu^2)} \text{ v independent of } w.\]

In these equations, \(i\) indexes patients and \(t\) indexes time. \(C_i\) and \(D_i\) are random slopes of early- and late-phase time at the patient level. The interaction term coefficients, \(E_{\text{early}}\) and \(E_{\text{late}}\), estimate the effects of treatment on the slope of NRS vs time during the early and late phases, respectively. The estimated slope of the late phase in the UC group is \(D\), and that in the PCA group is \(D+E_{\text{late}}\).

The \(z\) test of \(E_{\text{late}}\) is the test of the null hypothesis of no effect of treatment on the slope of NRS in the 30- to 120-minute period.

APPROACH TO SUBGROUP ANALYSES

For results disaggregated by pain location, the equations are:

\[
NRS_{it} = b_0 + b_1 \text{group}_i + b_2 \text{Weiler}_i + b_3 \text{JMC}_i \\
+ b_4 \text{Penn}_i + b_5 \text{abdominal}_i + C_i \text{early}_i + D_i \text{late}_i \\
+ E_{\text{early-early}}_i \times \text{group}_i + E_{\text{late-late}}_i \times \text{group}_i \\
+ f_1 \text{abdominal}_i \times \text{early}_i + f_2 \text{abdominal}_i \times \text{late}_i \\
+ g_1 \text{abdominal}_i \times \text{group} \times \text{early}_i + g_2 \text{abdominal}_i \times \text{group} \times \text{late}_i + u_i + \epsilon_{it},
\]

\[u \equiv N(0, \sigma^2) \text{ iid, } \epsilon \equiv N(0, \tau^2) \text{ iid, } u \text{ independent of } \epsilon.
\]

\[C_i = C + v_i; \ D_i = D + w_i; \ v \equiv N(0, \nu^2) \text{ iid, } w \equiv N(0, \varphi^2), \vphantom{N(0, \nu^2)} \text{ v independent of } w.
\]

In this case, the estimated slopes are given by the combinations of coefficients shown below.

<table>
<thead>
<tr>
<th>Period</th>
<th>Study Arm</th>
<th>Pain Location</th>
<th>Coefficient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>UC</td>
<td>Other</td>
<td>C+f1</td>
</tr>
<tr>
<td>Early</td>
<td>UC</td>
<td>Abdominal</td>
<td>C+g1</td>
</tr>
<tr>
<td>Early</td>
<td>PCA</td>
<td>Other</td>
<td>C+g2</td>
</tr>
<tr>
<td>Early</td>
<td>PCA</td>
<td>Abdominal</td>
<td>D+f1+g1</td>
</tr>
<tr>
<td>Late</td>
<td>UC</td>
<td>Other</td>
<td>D+f2</td>
</tr>
<tr>
<td>Late</td>
<td>PCA</td>
<td>Abdominal</td>
<td>D+E_{late}+g2</td>
</tr>
<tr>
<td>Late</td>
<td>PCA</td>
<td>Other</td>
<td>D+E_{late}+g2</td>
</tr>
</tbody>
</table>

The late-phase effect of PCA vs UC in abdominal pain is then \(D+E_{\text{late}}+g_2-(D+f_2)\), or simply \(E_{\text{late}}+g_2\). Similarly, among patients with pain in “other” locations, the late-phase effect of PCA vs UC is \(D+E_{\text{late}}=D_{\text{late}}\).

The \(z\) test of \(E_{\text{late}}+g_2\) is the test of the null hypothesis of no difference in the effect of treatment on the slope of NRS between patients with and without abdominal pain.

The approach toward site-specific results is similar, although with 4 sites, a greater number of terms and coefficients are involved.
**SENSITIVITY ANALYSES**

**Table E1.** Rate of decline of numeric rating scale score 30 to 120 minutes postbaseline by treatment group—robustness to treatment of missing data.

<table>
<thead>
<tr>
<th>Group</th>
<th>PCA Rate of Decline (95% CI)</th>
<th>UC Rate of Decline (95% CI)</th>
<th>Difference Rate of Decline (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis†</td>
<td>1.30 (1.00 to 1.61)</td>
<td>0.27 (-0.02 to 0.56)</td>
<td>1.03 (0.61 to 1.45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Last observation carried forward</td>
<td>1.21 (0.92 to 1.51)</td>
<td>0.33 (0.04 to 0.61)</td>
<td>0.89 (0.48 to 1.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Best (lowest) observation imputed</td>
<td>1.22 (0.92 to 1.51)</td>
<td>0.27 (-0.01 to 0.56)</td>
<td>0.94 (0.54 to 1.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Worst (highest) observation imputed</td>
<td>1.12 (0.81 to 1.43)</td>
<td>0.18 (-0.12 to 0.48)</td>
<td>0.94 (0.51 to 1.37)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Value shown in the “Difference” column may not equal the result from subtracting values in the PCA and UC columns because of rounding.
†Rate of decline estimated from regression coefficients for treatment, time, and interaction between treatment and time multiplied by 1.5.