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

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Abstract

Objective—To assess the effectiveness of patient controlled analgesia (PCA) in the Emergency Department (ED). We hypothesized that decline in pain intensity from 30 to 120 minutes after initial IV opioid administration is greater in patients receiving morphine via PCA compared to usual care (UC) and would differ by a clinically significant amount.

Method—Pragmatic randomized controlled trial of PCA and UC (opioid and dose at physician's discretion) in 4 EDs. Entry criteria included age 18–65, acute pain requiring IV opioids. The primary outcome was decline in numerical rating scale (NRS) pain score 30 to 120 minutes post-baseline. Secondary outcomes included satisfaction, time to analgesia, adverse events, and PCA 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 NRS units.

Results—636 patients were enrolled. The rate of decline in pain from 30 to 120 minutes was greater in patients receiving PCA than UC (difference=1.0 NRS units, 95% CI: 0.6, 1.5; $p<0.001$) but did not reach the threshold for clinical significance. More patients receiving PCA were satisfied with pain management (difference=9.3%, 95% CI: 3.3%, 15.1%). Median time to initial analgesia was 15 minutes longer for PCA than UC (95% CI: 11.4, 18.6). There were 7 adverse events in the PCA group, 1 in the UC group (difference=2.0%, 95% CI: 0.04%, 3.9%) and 11 pump programming errors.

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Conclusion—The findings of this study do not favor PCA over usual ED care for acute pain management.

Keywords

patient controlled analgesia; analgesia; emergency medicine; adult; opioid

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 EDs.³

Use of patient controlled analgesia (PCA) may be a more feasible alternative to clinician-driven titration and re-dosing. PCA enables patients to self-administer small intravenous boluses of an analgesic at pre-determined doses and frequency. It has the potential to address inter-individual variation in analgesic need as well as features of the ED environment that compromise individualized attention to pain management.³

PCA is used extensively in post-operative care. A Cochrane review of 49 randomized controlled trials (RCT) of PCA versus conventional administration found that pain control and satisfaction were higher in the PCA groups.⁴ Published data on ED PCA usage is limited. Two small studies found no differences when substituting PCA for time-intensive nurse titration of IV opioids (1–2 mg morphine boluses over time until adequate pain relief). Authors of both studies concluded that PCA is as effective and may be used in place of individual titration of IV morphine by a nurse.^{5, 6} However individual titration by clinical staff is unlikely to constitute usual ED care.

The authors of two recently conducted randomized trials comparing PCA to routine care in ED patients found significantly less pain over a 12-hour period in patients with abdominal pain treated with PCA but not in patients with pain from trauma.^{7, 8}

We previously conducted a randomized trial of PCA in ED patients with abdominal pain.⁹ Patients in the PCA group received a loading dose of 0.1mg/kg IV morphine 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 1.5 NRS unit greater decline in pain from 30 to 120 minutes in patients treated with PCA. More patients receiving PCA were satisfied with their pain treatment. There were no differences in the incidence of side effects or adverse events. This prior study, designed to evaluate ED PCA 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 prior findings to more naturalistic conditions with PCA initiated and monitored by ED nurses, initial IV 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 PCA use is demonstrated to be more effective than UC 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 PCA 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 the difference would be clinically significant. A value of 1.3 NRS units has been used as a standard definition of a clinically significant difference between treatment groups.¹⁰ 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.

METHODS

Study Design and Setting

This is a multi-center randomized controlled trial of PCA versus usual care (UC). The study was registered with ClinicalTrials.gov (Identifier NCT01775371) and approved by the institutional review board of Albert Einstein College of Medicine. The National Institute of Nursing Research provided funding (1R01NR013980). Data were collected from 4/30/2013 through 2/25/2016.

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

Selection of Participants

Patients 18 to 65 years of age, whose ED physician planned to administer IV opioid analgesics and was amenable to using PCA, were eligible for inclusion during hours when research associates (RA) were available. RA coverage varied by site ranging from 8:00 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 one 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/abuse; altered mental status/intoxication; were expected to require procedural sedation; were pregnant or

breast-feeding; had a history of chronic obstructive pulmonary disease, sleep apnea; baseline oxygen saturation (room air) < 97%; systolic blood pressure < 100 mm Hg; use of specific medications (benzodiazepines, monoamine oxidase inhibitors, phenothiazines, or tricyclic antidepressants); history of renal insufficiency/failure; morphine allergy; inability to provide informed consent; inability to understand/operate PCA device; or previous study entry.

RAs 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 IV opioids, the RA described the study and oral consent was obtained for additional eligibility screening. If eligible, the RA obtained written informed consent and HIPAA authorization.

A randomization allocation schedule with 25 blocks of 10 patients for each site was generated using a random plan generator (www.randomization.com). Randomly allocated assignments were placed in opaque, sealed, consecutively numbered envelopes or uploaded into the electronic data entry system depending on study site.

Interventions

The intervention for the PCA group consisted of: a loading dose of 0.1 mg/kg IV morphine; demand dose of 1 mg IV morphine; lock-out interval (time from the end of delivery of one dose until time the device will respond to another demand for analgesia) of 6 minutes; and physician-managed analgesic supplementation as needed. The ED nurse programmed the pump, instructed patients in its use, and administered the loading dose through the pump. PCA was paused if patients left the ED for any reasons, such as imaging tests.

The UC group received an IV 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 PCA pump used at JMC was the MOOG/Curlin PainSmart™ IOD ambulatory infusion system (Moog Medical Devices Group, Buffalo, NY). Montefiore sites used the Hospira Gemstar™ Infusion System (Hospira Inc., San Jose, CA). UPenn used the Hospira LifeCare™ PCA Infusion System (Hospira Inc., San Jose, CA).

PCA was not in routine use in the JMC 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 PCA use. PCA was already in use for sickle cell patients at the Montefiore EDs and treatment of trauma patients at UPenn. Nursing staff at these sites had previously received PCA competency training upon hiring. Nurses at these sites received information about the study but did not undergo additional training.

Methods and Measurements

After randomization the RAs 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 post-baseline, the RAs asked patients to rate their pain intensity on a verbally administered numerical rating scale (NRS),

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 RAs measured oxygen saturation via pulse oximetry, blood pressure, heart rate and respiratory rate at baseline and every 15 minutes thereafter up to 120 minutes. Every 30 minutes the RAs asked patients about nausea, vomiting, and pruritis and observed the level of sedation using a modified Ramsay Sedation Scale.¹² At the end of the study the RAs 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 as per nursing protocol and used them as they would in usual practice. Vital sign measurements obtained by the RAs meeting criteria for adverse events were reported immediately to clinical staff.

The RAs collected information about drug, dose, and time of physician-initiated administration of analgesics from the electronic medical record. The dose of hydromorphone, the only IV opioid administered other than morphine, was converted to morphine equivalent units (1 mg hydromorphone = 7 mg morphine).¹³ The RAs 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 PCA pump was recorded automatically and electronically retrieved from the pump.

PCA malfunctions were observed and documented by the RAs. PCA operator error was determined by systematic review of all pump output after an RA brought an operator error to the investigators’ attention.

Outcomes

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 post-initial opioid dose. Secondary outcomes included patient satisfaction with pain management, preference for 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 RA ascertained the patient met basic inclusion criteria. Side effects were incidence of nausea, vomiting, pruritis, 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 < 92% on room air, respiratory rate < 10 breaths/minute, systolic blood pressure < 90 mm Hg, PCA device malfunction, and PCA operator error.

Analysis

Characteristics of the sample are reported as mean and standard deviation, 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 NRS pain scores from 30 to 120 minutes

by treatment group. Fixed effects in the analysis include 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 using a z-test of the coefficient of the treatment group by time interaction term (details in the technical appendix).

Two additional planned analyses were conducted to determine whether treatment effect differed by study site and location of pain (abdominal versus non-abdominal). 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 NRS scores over time by study site and pain location. All models were fitted using maximum likelihood estimation. A nominal significance criterion of 0.05 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 NRS units) we converted the rates of decline per hour to reflect the 90 minute time period from 30 to 120 minutes. These rates of decline are calculated by combining the applicable regression coefficients (time, group, and group by time interactions, as appropriate), and multiplying by 1.5 to change NRS units from per hour to units per 90 minutes.

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

Missing data: Each patient is included in the analysis to the extent that data are present. We tested the robustness of the primary analysis by carrying out multiple sensitivity analyses with imputation of missing observations (details in technical appendix).

All analyses were performed as intention to treat.

Sample size

The sample size was designed to detect with high probability a difference between study groups that corresponds to a clinically significant difference in pain over time. A mean difference of 1.3 units on the NRS pain scale is considered to be the minimal clinically significant difference between group pain scores.¹⁰ Because the period between 30 and 120 minutes is 1.5 hours, a difference between slopes of 0.87 per hour represents a difference of 1.3 NRS units over the 30 to 120 minute period. We carried out Monte Carlo simulations of our study design and analysis to estimate statistical power. In order to achieve 0.95 power to detect a difference in slope per hour of 0.87 NRS units at the 0.05 significance level, approximately 150 patients are needed in each treatment group. Because we were interested in whether the effect observed in the earlier study⁹ generalizes 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) provides 0.82 power to detect a difference if the pain location-specific effects of PCA vs UC differ by 0.8 per hour.

This provides power of 0.99 to detect a site-specific difference of 0.8 NRS units per hour between groups.

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 pregnancy or breast-feeding. Of the 4,036 patients not randomized, 267 patients (6.6%) were excluded because the attending physician did not think the patient “warranted PCA” or “was a good candidate for PCA”. Ninety-one patients (2%) were excluded because the physician planned to give one small bolus of IV 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”, “want pain medication immediately”. More patients receiving PCA were missing data after intervention (25) than UC (7). This was due primarily to the need to stop PCA when they left the ED for imaging studies.

The sample was predominantly female and Hispanic (Table 1). Three-quarters had abdominal pain and most had severe pain (pain score >7).¹⁴ The treatment groups were well matched on background characteristics. 317 patients were enrolled at JMC, 192 at Moses, 106 at Weiler, and 21 at UPenn.

Table 2 shows the amount of IV opioid patients in the two groups received in morphine equivalent units. The initial medication was hydromorphone for 9% of the UC patients. The initial dose given to patients in the PCA group was higher than UC as was the total amount of opioid received. Time from screening to initial bolus of opioid was longer for the PCA group than UC. The PCA median time to treatment was 45 minutes, the UC median time was 30 minutes (difference: 15 min, 95% CI: 11.4, 18.6 minutes).

There was a large decrease in pain of similar magnitude in both groups from baseline to 30 minutes (Figure 2). Between 30 and 120 minutes, pain in the UC group plateaued, while pain continued to decline in patients treated with PCA as shown in Figure 2. The difference between mean rate of decline in the two groups over the 90-minute period was 1.0 NRS units (95% CI: 0.6, 1.5; $p < 0.001$) (Table 3). This was less than the 1.3 NRS unit magnitude specified a priori to represent a clinically significant difference. The results of the sensitivity analyses were similar to the primary analysis (Table in the technical appendix). There was no statistically significant difference in treatment effect by site or location of pain (Table 3). PCA compared favorably to UC on all secondary measures of effectiveness (table 4).

The incidence of side effects was similar (Table 5) in the two treatment groups. Adverse events were more common in patients receiving PCA (Table 5). Seven patients who received PCA experienced adverse events (2.3%) compared to one who received UC (0.3%) (difference: 2.0%; 95% CI: 0.04%, 3.9%). Four patients who received PCA experienced hypotension that resolved spontaneously or with IV fluids. One of these patients also received supplemental oxygen for transient decrease in pulse oximetry to 88%. Two additional patients with PCA received supplemental oxygen for pulse oximetry readings of

91% and 93% respectively and one had PCA halted for oxygen saturation of 88%. One patient in the UC group had a transient reading of 88% on room air. All events resolved with the interventions noted within the two-hour study period. No patient had a respiratory rate less than 10 breaths/minute 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 over the two-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 PCA order set to explicitly specify no background infusion.

LIMITATIONS

Blinding of treatment group was not considered desirable or feasible in this study for several reasons. First, subjects' experience with the modality of analgesia administration itself (PCA versus UC) could only be accomplished if patients were aware of treatment assignment. Second, blinding would require subjects in significant pain to receive sham dosing on a PCA pump which was felt 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 due to slower than expected recruitment. Further, the patients we enrolled were not evenly divided among the sites. While we had more than adequate power to test the effectiveness of PCA 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 three planned analyses in the total sample, site and location of pain, the inferences would have been unchanged.

Resources did not permit 24/7 RA coverage. However, consecutive samples of patients were enrolled during the hours research staff was available.

The full benefit of PCA may accrue over a longer period of time than observed during the two-hour duration of the study. While this duration might be expected to be adequate to capture the ability of PCA to address inter-individual variability in initial opioid requirement, it may not be long enough to capture the full benefit of access to re-dosing in response to the diminishing effect of initial analgesic dose over time.

DISCUSSION

This randomized trial provides a pragmatic assessment of ED PCA by evaluating effectiveness in a broad sample of ED patients with pain requiring IV 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 NRS units, failed to meet the threshold set a priori for clinical significance despite patients in the PCA group receiving a higher amount of opioid than patients who received UC. This leads to a different inference about ED PCA effectiveness than our prior one-site study of efficacy in which we found a clinically significant difference of 1.5 NRS units in patients with abdominal pain.⁹

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 prior study, 1.5 NRS units, met the threshold for clinical significance, while at the two other sites with sufficient numbers of patients to make precise estimates, it did not, 0.3 NRS units and 0.8 NRS units. The variability of these estimates suggests there may be a heterogeneous effect of PCA at different sites however our study did not have adequate power to make this conclusion due to 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 NRS units, and pain at other locations, 0.5 NRS units, met the criterion for clinical significance and the interaction term was not statistically significant. Smith, et al. recently conducted a randomized trial comparing PCA to routine care in ED patients with moderate to severe abdominal pain and pain from trauma.^{7, 8} They found significantly less pain over a 12-hour period in patients with abdominal pain treated with PCA 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 as the authors report effectiveness as difference between area under the curve of pain measurements over 12 hours.

The modest PCA effect in our study mirrors the results of post-operative studies. In a meta-analysis of studies of post-operative pain in the first 24 hours after surgery, McNicol, et al. found a mean difference of 9 mm less pain on a 100 mm VAS pain scale in patients treated with PCA.⁴

Smith's study of abdominal pain, like our own, documented greater patient satisfaction with PCA than the comparison groups.⁷ The meta-analysis of studies of patients treated with PCA post-operatively had similar results.⁴ McNicol posits this may be due to greater autonomy over pain control and reduced fear of not obtaining sufficient analgesia.

Seven patients in the present study who received PCA experienced adverse events (2.3%) versus 1 UC patient (0.3%). While these adverse events resolved with minimal or no intervention, the excess incidence of these events is concerning. The meta-analysis of post-operative studies found the incidence of respiratory depression (composite measure including respiratory rate less than 10 breaths per minute and oxygen saturation less than 90%) to be similar between PCA and comparison groups, 2.3% versus 2.0%.

There were 11 instances when a pump was erroneously programmed to give constant background infusions. While no associated adverse events occurred, potential for harm from this type of error increases with time. PCA medication errors in post-operative studies have

been documented although rates of error are difficult to quantify.¹⁵ Published recommendations to maximize safety include simplification of pump interface, use of pump-stored protocols, use of standard medication concentration, on-going staff training, patient education, and policy requiring a second caregiver to review pump programming.¹⁶

In summary, in this pragmatic trial, the difference in effectiveness between PCA 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 do not favor PCA over usual care for acute pain management in the ED.

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Technical Appendix

Details of Primary Analysis

The primary analysis is based on a random slopes linear model of NRS score. In this model, time is represented as two 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 patient controlled anesthesia (PCA) and 0 for usual care (UC). Pain location is also dichotomous, abdominal = 1, other location = 0. The study site variable, site, is a four level variable coded 1 = Moses, 2 = Weiler, 3 = JMC, 4 = Penn. This four-level variable is in turn incorporated in the model as three dichotomous indicator variables, the reference category being Moses.

The model equations for the primary analysis are:

$$\begin{aligned} \text{NRS}_{it} = & b_0 + b_1 \text{group}_i + b_2 \text{Weiler}_i + b_3 \text{JMC}_i + b_4 \text{Penn}_i + b_5 \text{abdominal}_i + C_i \text{early}_t + D_i \text{late}_t + \\ & E_{\text{early}} \text{early}_t \times \text{group}_i + E_{\text{late}} \text{late}_t \times \text{group}_i + u_i + \varepsilon_{it}, \\ & u \sim N(0, \sigma^2) \text{ iid}, \varepsilon \sim N(0, \tau^2) \text{ iid}, u \text{ independent of } \varepsilon. \\ & C_i = C + v_i; D_i = D + w_i, v \sim N(0, v^2) \text{ iid}, w \sim N(0, \phi^2), v \text{ independent of } w. \end{aligned}$$

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_{early} and E_{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_{late} is the test of the null hypothesis of no effect of treatment on the slope of NRS in the 30–120 minute time period.

Approach to subgroup analyses

For results disaggregated by pain location the equations are:

$$\begin{aligned} \text{NRS}_{it} = & b_0 + b_1 \text{group}_i + b_2 \text{Weiler}_i + b_3 \text{JMC}_i + b_4 \text{Penn}_i + b_5 \text{abdominal}_i + C_i \text{early}_t + D_i \text{late}_t + \\ & E_{\text{early}} \text{early}_t \times \text{group}_i + E_{\text{late}} \text{late}_t \times \text{group}_i + f_1 \text{abdominal}_i \times \text{early}_t + f_2 \text{abdominal}_i \times \text{late}_t + \\ & g_1 \text{abdominal}_i \times \text{group} \times \text{early}_t + g_2 \text{abdominal}_i \times \text{group} \times \text{late}_t + u_i + \varepsilon_{it}, \\ & u \sim N(0, \sigma^2) \text{ iid}, \varepsilon \sim N(0, \tau^2) \text{ iid}, u \text{ independent of } \varepsilon. \\ & C_i = C + v_i; D_i = D + W_i, v \sim N(0, v^2) \text{ iid}, w \sim N(0, \phi^2), v \text{ independent of } w. \end{aligned}$$

In this case, the estimated slope s are given by the combinations of coefficients shown below

Time Period	Study Arm	Pain Location	Coefficient(s)
Early	UC	Other	C
Early	UC	Abdominal	C+f ₁
Early	PCA	Other	C + E _{early}
Early	PCA	Abdominal	C + E _{early} + f ₁ + g ₁
Late	UC	Other	D
Late	UC	Abdominal	D+f ₂
Late	PCA	Other	D + E _{late}
Late	PCA	Abdominal	D + E _{late} + f ₂ + g ₂

The late-phase effect of PCA vs UC in Abdominal Pain is, then $D+E_{late}+f_2+g_2-(D+f_2)$, or simply $E_{late}+g_2$. Similarly, among those with pain in Other locations, the late-phase effect of PCA vs UC is $D+E_{late}-D=E_{late}$.

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

The approach towards site-specific results is similar, though, with four sites, a greater number of terms and coefficients are involved.

Sensitivity Analyses

Table

Rate of Decline of NRS Score 30 to 120 minutes Post-Baseline by Treatment Group—
Robustness to treatment of Missing Data

Group	PCA Rate of Decline (95% CI)	Usual Care Rate of Decline (95% CI)	Difference Rate of Decline (95% CI)	p
Primary Analysis ^a	1.30 (1.00, 1.61)	0.27 (−0.02, 0.56)	1.03 (0.61, 1.45)	<0.001
Last Observation Carried Forward	1.21 (0.92, 1.51)	0.33 (0.04, 0.61)	0.89 (0.48, 1.30)	<0.001
Best (Lowest) Observation Imputed	1.22 (0.92, 1.51)	0.27 (−0.01, 0.56)	0.94 (0.54, 1.35)	<0.001
Worst (Highest) Observation Imputed	1.12 (0.81, 1.43)	0.18 (−0.12, 0.48)	0.94 (0.51, 1.37)	<0.001

^a rate of decline estimated from regression coefficients for treatment, time, and interaction between treatment by time multiplied by 1.5

Note: Value shown in Difference column may not equal result from subtracting values in PCA and UC columns due to rounding.

Figure 1.
Patient Flow Diagram

Figure 2. Pain Intensity Scores at Each Time Point. Horizontal lines indicate mean pain intensity. A. Scores of patients who received PCA; B. Scores of patients who received usual care. A random value has been added to each score in order to display overlapping scores

Table 1

Characteristics of the Sample

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

Table 2Dose of Opioid Analgesics in Morphine Equivalent Units (MEU)^a

	PCA N=306	UC N=330	Difference (95% CI)
Initial dose (mg) Mean (SD)	8.0 (1.4)	5.1 (2.0)	2.9 (2.6,3.2)
Additional dose in 30 minutes after initial dose Mean (SD)	0.8 (1.2)	0.1 (0.5)	0.8 (0.6,0.9)
Additional dose 30 minutes to 120 minutes after initial dose Mean (SD)	3.2 (3.6)	1.0 (2.1)	2.2 (1.7, 2.6)
Total dose Mean (SD)	12.0 (4.3)	6.1 (2.9)	5.9 (5.2, 6.4)

^a 1 mg morphine = 1 MEU; 1 mg hydromorphone=7 mg MEU 3

Table 3

Rate of Decline of NRS Score 30 to 120 minutes Post-Baseline by Treatment Group

Group	PCA Rate of Decline (95% CI)	Usual Care Rate of Decline (95% CI)	Difference between Rates of Decline (95% CI)	p
All Patients ^a	1.3 (1.0, 1.6)	0.3 (0.0, 0.6)	1.0 (0.6, 1.5)	<0.001
Site ^b				0.09
Moses	1.1 (0.6, 1.7)	0.8 (0.3, 1.4)	0.3 (−0.5, 1.1)	
Weiler	1.0 (0.2, 1.8)	0.2 (−0.5, 0.9)	0.8 (−0.2, 1.8)	
JMC	1.5 (1.1, 2.0)	0.0 (−0.4, 0.4)	1.5 (0.9, 2.1)	
Penn	1.2 (−0.5, 2.9)	−0.6 (−2.2, 1.1)	1.8 (−0.6, 4.2)	
Pain Location ^c				0.17
Abdominal	1.3 (1.0, 1.7)	0.1 (−0.2, 0.5)	1.2 (0.7, 1.7)	
Other Location	1.3 (0.6, 1.9)	0.8 (0.2, 1.4)	0.5 (−0.4, 1.4)	

^aRate of decline estimated from regression coefficients for treatment, time, and interaction between treatment by time multiplied by 1.5^bRate of decline estimated from regression coefficients for treatment, time, site and interaction between treatment by time, interaction between site and time, interaction between time, treatment, and site multiplied by 1.5^cRate of decline estimated from regression coefficients for treatment, time, pain location and interaction between treatment by time, interaction between pain location and time, interaction between time, treatment, and pain location multiplied by 1.5

Table 4

Secondary Measures of Effectiveness at 120 minutes Post-baseline

	PCA N (%)	UC N (%)	Difference % (95% CI)
Satisfaction at 120 minutes ^a			
Satisfied	247/281 (87.9)	254/323 (78.6)	9.3 (3.3, 15.1)
Prefer same treatment in future ^b			
Yes	252/279 (90.3)	266/322 (82.6)	7.7 (2.2, 13.1)
Want more pain medication at 120 minutes ^c			
Yes	69/278 (24.8)	131/321 (40.8)	-16.0 (-23.3, -8.5)

^aSatisfied or very satisfied versus very unsatisfied, unsatisfied, neutral in response to the question "How satisfied are you with the result of your pain treatment overall?"

^bIn 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?"

^cIn response to the question: "Do you want more pain medication?"

Table 5

Side effects and Adverse Events by Group

	PCA N (%)	UC N (%)	Difference (95% CI)
Nausea ^a	25/115 (21.7)	22/121 (18.2)	3.6 (−6.7, 13.7)
Vomiting ^a	7/115 (6.1)	3/121 (2.5)	3.6 (−1.9, 9.1)
Pruritis	29/306 (9.5)	37/330 (11.2)	−1.7 (−6.6, 3.1)
Sedation ^b	17/306 (5.6)	26/330 (7.9)	−2.3 (−6.2, 1.6)
Adverse events	7/306 (2.3)	1/330 (0.3)	2.0 (0.04, 3.9)

^a Among patients not nauseated or vomiting before treatment

^b Sluggish response to glabellar tap or loud sound or no response. The one patient with no response received usual care.