Randomized Clinical Trial Comparing a Patient-Driven Titration Protocol of Intravenous Hydromorphone With Traditional Physician-Driven Management of Emergency Department Patients With Acute Severe Pain

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Study objective: We test the null hypothesis that the “1+1” hydromorphone patient-driven protocol is clinically and statistically equivalent in safety and efficacy to that of traditional physician-driven administration of opioids for emergency department (ED) treatment of acute severe pain.

Methods: This was a prospective randomized clinical trial of nonelderly adults presenting to an urban academic ED with acute pain of sufficient severity to warrant intravenous (IV) opioids in the judgment of the attending physician. Patients randomized to the 1+1 hydromorphone patient-driven protocol received 1 mg IV hydromorphone followed by a second 1-mg dose 15 minutes later if the patient responded affirmatively to the question, “Do you want more pain medication?” Patients in the physician-driven group received any IV opioid in the dose chosen by the ED attending physician, with any additional analgesia provided at the discretion of that physician. The primary outcome was the difference in improvement in pain between the 2 groups at 60 minutes, as measured by a validated and reproducible numeric rating scale. Secondary outcomes included incidence of oxygen desaturation, hypoventilation, hypotension, bradycardia, nausea, vomiting, pruritus, and use of naloxone.

Results: The mean decrease in numeric rating scale pain scores for the 1+1 hydromorphone patient-driven group was 5.6 versus 4.5 in the physician-driven group. The difference of 1.1 numeric rating scale units (95% confidence interval 0.3 to 1.9) was statistically significant but fell 0.2 numeric rating scale units short of the 1.3 numeric rating scale unit threshold required to attain clinically significant efficacy. Safety profiles were similarly satisfactory in both groups. Ninety-four percent of the 1+1 hydromorphone patient-driven group achieved adequate analgesia (as defined by the patient) within 60 minutes of protocol initiation.

Conclusion: The 1+1 hydromorphone patient-driven protocol is statistically superior and at least as clinically efficacious and safe as traditional physician-driven treatment of ED patients with acute severe pain. More than 9 of 10 patients randomized to the study protocol achieved satisfactory pain control, as defined by the patient, within an hour or less. [Ann Emerg Med. 2009;54:561-567.]

INTRODUCTION

Background

It is widely recognized that there is large interindividual variability in the amount of opioids needed to control pain.1-3 Although individualized titration of intravenous (IV) opioids is the criterion standard for the treatment of acute pain, this may not be practical in many high-volume emergency departments (EDs) under conditions of crowding. We developed the “1+1” hydromorphone protocol4 as an easily remembered patient-driven method of rapidly obtaining pain relief that takes into account individualized treatment and the reality of crowded EDs. In this protocol, patients received an initial dose of 1 mg IV hydromorphone, followed by an optional second dose of 1 mg IV hydromorphone 15 minutes later if they responded affirmatively when asked whether they want more pain medication.

In a previous study we showed that the 1+1 hydromorphone protocol is both a safe and efficacious strategy for acute pain.
Editor’s Capsule Summary

What is already known on this topic
A pain management protocol of administering 1 mg of hydromorphone intravenously (IV) followed by a second 1-mg dose 15 minutes later (if needed) has been shown to be safe and effective in nonelderly adults.

What question this study addressed
Does this “1+1” protocol safely achieve superior pain relief over usual treatment without a protocol?

What this study adds to our knowledge
In this randomized study of 224 subjects, those in the 1+1 protocol group safely received more opioids and demonstrated greater improvement in pain scores.

How this might change clinical practice
The hydromorphone 1+1 protocol is a safe and effective way to treat pain in nonelderly adults and appears superior to usual care without a protocol.

Management in the ED. In this randomized trial, we wished to compare the pain relief provided by the 1+1 hydromorphone patient-driven protocol to that of traditional physician-driven administration of IV opioids for treatment of acute pain. Because of the longstanding problem of undertreatment of pain, development and testing of protocols to optimize ED pain management is clinically important.

MATERIALS AND METHODS

Study Design

This was a randomized clinical trial designed to test the null hypothesis that the 1+1 hydromorphone patient-driven protocol is clinically and statistically equivalent in safety and efficacy to that of traditional physician-driven administration of opioids for ED treatment of acute severe pain. The study was approved by the Montefiore Medical Center institutional review board.

Setting

The study was conducted in an adult academic ED located in an inner-city environment with a census of approximately 100,000 patients per year.

Selection of Participants

The study population consisted of patients aged 21 to 64 years, presenting to the ED with acute pain (defined as pain of fewer than 7 days duration) of sufficient severity to warrant use of IV opioids in the judgment of an American Board of Emergency Medicine certified attending physician. Exclusion criteria were patients whose primary providers were part of the research group, allergy to hydromorphone or morphine, systolic blood pressure less than 90 mm Hg, room air oxygen saturation by pulse oximetry less than 95% at baseline, alcohol or other drug intoxication as judged by the attending physician, use of other opioids within the past 7 days, use of a monoamine oxidase inhibitor, weight less than 100 pounds, pregnancy, and presence of a chronic pain syndrome (such as sickle cell disease or fibromyalgia).

The treating clinic or nurse referred eligible patients to trained, fluent, bilingual (English/Spanish) research associates who consented and enrolled subjects 24 hours per day, 7 days per week, from December 2007 to March 2008.

Interventions

After written informed consent was obtained (in either English or Spanish), enrolled patients were randomly allocated to the 1+1 hydromorphone patient-driven group or the physician-driven group. The assignments were generated by an online random-number generator (available at http://www.randomization.com) and placed in sealed opaque envelopes that were opened in sequential order by the research associates.

Patients in the 1+1 hydromorphone patient-driven group received an initial dose of 1 mg IV hydromorphone. Fifteen minutes later, these patients were asked by the research associates the following question: “Do you want more pain medication?” If patients answered yes, they received an additional dose of 1 mg IV hydromorphone. If patients answered no, they did not receive additional pain medication at that time. Patients in the physician-driven group received a dose of an IV opioid, the type and dose of which were determined by the treating physician and which could include IV hydromorphone. Unlike the 1+1 hydromorphone patient-driven group, patients in the physician-driven group were not asked at 15 minutes whether they wanted more pain medication because this more closely parallels usual pain management in our ED.

Patients were enrolled after physician evaluation in the ED. Additional pain medications could be requested by patients at any point throughout the study. Antiemetics were given only in response to symptoms. Administration of additional analgesics and antiemetics was tracked for the duration of the study.

Methods of Measurement

Subjects were asked to rate their pain on a previously validated and reproducible numeric rating scale that ranged from 0 (“no pain”) through 10 (“worst pain possible”). Pain scores were recorded at baseline, every minute for the first 5 minutes, and at 15, 30, and 60 minutes after completion of the first administration of opioid. Patients who received additional IV opioids again had pain measurements recorded every minute for 5 minutes and at 15, 30, and 60 minutes after completion of the second administration of opioid.
The dose of opioids was estimated by calculating the morphine analgesic equivalent dose of hydromorphone as 7 mg morphine=1 mg hydromorphone.

Oxygen saturation and respiratory rate were measured at all time points. Pulse rate, systolic blood pressure, nausea, vomiting, and pruritus were measured at 5, 15, 30, and 60 minutes after completion of the initial administration of opioid and again after completion of the second administration of opioid if given. Adverse events were defined as oxygen saturation less than 95%, systolic blood pressure less than 90 mm Hg, respiratory rate less than 12 breaths/min, pulse rate less than 60 beats/min, and use of naloxone at any time during or after the study.

Data Collection and Processing

Data were collected on a standardized data collection instrument and entered weekly into the program SPSS Data Entry (SPSS, Inc., Chicago, IL) by a trained data clerk. Double entry of the entire data set was performed by a second trained clerk, and any differences were reconciled by referral to the original data collection instrument. Data quality was also assessed by random selection of 10% of data collection instruments for auditing.

Outcome Measures

The primary efficacy outcome was decrease in pain from baseline to 60 minutes postbaseline. The primary safety outcome was desaturation below 95% at any time during the study. Secondary outcomes included percentage of patients whose pain scores decreased by 3 numeric rating scale points or more, adverse events (hyperventilation, hypotension, bradycardia, nausea, vomiting, or pruritus) that occurred within the 60-minute period of measurement, use of naloxone at any time, and initial and total dose of opioids.

Primary Data Analysis

Descriptive statistics were calculated for all variables. All statistics are shown as means or proportions with 95% confidence intervals (CIs). We used Wilson’s method of calculating 95% CIs around the differences between proportions. In addition, P values are shown for the 2 primary outcomes (change in pain baseline to 60 minutes postbaseline and percentage of patients who had oxygen desaturation at any point during the study). We have presented mean change in the numeric rating scale scores so that our statistics can be compared with those of the many studies that have reported mean change. However, because of the non-normal distribution of the primary outcome, we have used the Mann-Whitney U test to calculate the statistical significance of the null hypothesis that the distributions of change are equal. Tests were used to compare categorical change in pain of 3 or more numeric rating scale units. We used post hoc multiple linear regression to adjust for unexpected differences in baseline characteristics. Categorical variables that differed by 10% or more between groups were included as covariates in the multiple regression analysis.

Exploratory analyses were conducted that examined the change in pain in several subsets of patients: those who received 1 dose only, those who received 2 or 3 doses, and a comparison of pain in patients in the physician-driven care group who received only morphine.

SPSS version 15.01 was used to conduct all data analyses. A sample size of 112 patients per group was calculated with the following assumptions: significance criterion=0.05, power=0.90, difference between mean change in numeric rating scale=1.3, and SD=3.0. A numeric rating scale value of 1.3 has been found to be the minimal clinically significant difference in pain that can be detected by patients in several studies. These studies also indicate that the SD of this value is approximately 3.0 numeric rating scale units. nQuery Advisor version 6.0 (Los Angeles, CA) was used for sample size calculation.

RESULTS

As shown in the Table, with the Consolidated Standards of Reporting Trials (CONSORT) format recommended for randomized clinical trials, 494 subjects were approached and 224 were randomized. One hundred eight subjects randomized to the 1+1 hydromorphone patient-driven group and 110 patients randomized to the physician-driven group had sufficient data for analysis. The most frequent reasons for exclusion were age more than 65 years and use of opioids in the past 7 days.

The sample was predominantly women and Hispanic. More than half the patients had abdominal pain and reported their pain severity as 10, the highest score on the numeric rating scale. Despite randomization, there were chance differences between groups in the point estimates of several baseline features (Table 1).

Of the 32 (29%) patients in the 1+1 hydromorphone patient-driven group who wanted more analgesics 15 minutes after the first dose, 26 (81%) received the second dose within 60 minutes of the first bolus. Only 7 (6%) patients in the 1+1 hydromorphone patient-driven group reported that they wanted additional analgesics 15 minutes after they received their second dose. Thus 94% of the 1+1 hydromorphone patient-driven group achieved adequate analgesia (as defined by the patient) within 60 minutes of protocol initiation. Eleven (10%) patients in the physician-driven group received additional analgesics in the 1-hour period.

Table 2 shows the change in pain 60 minutes after baseline in the entire sample, as well as in 3 subsets: (1) all patients in the 1+1 hydromorphone patient-driven group compared with patients in the physician-driven group who received only morphine; (2) patients who received only 1 dose of analgesic; and (3) patients who received 2 or 3 doses of analgesics.

Patients in the 1+1 hydromorphone patient-driven group experienced a significantly greater decrease in pain than those in the physician-driven group (P<.01). However, the magnitude of the difference was 1.1 numeric rating scale units, which, although statistically significant, fell short of the previously established minimum clinically significant difference in pain of...
The findings were not affected by adjustment for disparities in baseline pain scores and location of pain. The distribution of change in pain in the 2 groups can be seen in Figure E1 (available online at http://www.annemergmed.com).

Expressed as morphine equivalent units, the mean total dose of opioids for patients who had 1 dose of opioids in the physician-driven group was 5.8 mg (95% CI 5.3 to 6.3) compared with 7.0 mg in the 1+1 protocol group. The mean total dose of opioids in the physician-driven group was 6.5 mg morphine equivalent units (95% CI 5.8 to 7.2) versus 8.7 (95% CI 8.1 to 9.3) for the 1+1 group. See Table E1 (available online at http://www.annemergmed.com) for the distribution of the doses.

Table 3 shows the incidence of adverse events, which was similar in both groups. Five patients (5%) in the 1+1 hydromorphone patient-driven group experienced desaturation (defined a priori as oxygen saturation <95%) 1 or more times after the first infusion and 4 (4%) in the physician-driven group. As per our protocol, all patients who experienced desaturation below 95% began receiving 4 L nasal cannula oxygen until study termination. All such patients responded immediately to nasal cannula oxygen, as evidenced by an increase in their oxygen saturation to greater than or equal to 95%, and did not require any further intervention.

LIMITATIONS

We asked the patient-centered question, “Do you want more pain medication” at 15 minutes to the 1+1 hydromorphone patient-driven group only. We reasoned that asking patients in the physician-driven group this question at 15 minutes would have represented a marked deviation from “usual care” in our ED. In a prospective, observational study of 842 ED patients in 20 US and Canadian EDs, reassessments of pain intensity were uncommon. Pain intensity was measured only once for most patients (at triage), without additional assessments that might reflect the effect of analgesic therapies.

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Treatment of pain in our physician-driven group may not have been representative of physician-driven usual care in other institutions for several reasons. First, because patients could be enrolled only if their ED attending physicians decided that they would treat the patients’ pain with an IV opioid, all patients in the physician-driven group received an IV opioid. Although such a design feature is likely to have attenuated the difference between the groups because of inherent bias toward the null, we wished to compare our 1/1001 hydromorphone protocol to optimized physician-driven care.

The study was not blinded. Thus, it is possible that attending physicians who were enthusiastic about hydromorphone consciously or unconsciously undertreated patients in the physician-driven group.

We have conducted a series of studies involving hydromorphone,4,17,21,22 which may explain why 26% of our physician-driven group received IV hydromorphone, thus further attenuating differences between the 2 groups. To assess this potential bias, we restricted one of our comparisons to patients who had received morphine only as their first dose. This analysis, shown in Table 2, did not affect the magnitude of the difference between groups.

To compare our results with those of other studies, we used standard measures of pain relief, including mean change in pain score and a cut point based on mean values.15,23,24 However, use of a patient-centered outcome that relies on individual decisions made by the patient about that individual’s wish to obtain further analgesia may be a more valid and straightforward indicator of adequacy of pain relief. We did not use that measure as our primary outcome for this study because we could not ask patients in the physician-driven group whether they wanted more analgesia without informing their physicians, thus potentially attenuating differences between the groups and further driving our findings toward the null.

Our results may not be generalizable to a broader population because our study was conducted in an inner-city hospital that primarily cares for minority and medically underserved patients. In addition, our results do not extend to patients 65 years of age and older.

**DISCUSSION**

The 2-step 1/1 hydromorphone patient-driven titration regimen that we tested led to statistically better acute pain

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### Table 2. Change in numeric rating scale pain intensity from baseline to 60 minutes.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>“1 + 1” Patient-Driven Group</th>
<th>Physician-Driven Group</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>N=108</td>
<td>N=110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in NRS score</td>
<td>5.6</td>
<td>4.5</td>
<td>1.1</td>
<td>0.3 to 1.9</td>
</tr>
<tr>
<td>Mean adjusted* change in NRS score</td>
<td>5.5</td>
<td>4.5</td>
<td>1.0</td>
<td>0.2 to 1.7</td>
</tr>
<tr>
<td>Percentage decrease ≥3 NRS units</td>
<td>84.3</td>
<td>74.6</td>
<td>9.7</td>
<td>-1.1 to 20.0</td>
</tr>
<tr>
<td><strong>1+1 Protocol and physician-driven group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in NRS score</td>
<td>5.6</td>
<td>4.4</td>
<td>1.2</td>
<td>0.34 to 2.10</td>
</tr>
<tr>
<td>Percentage decrease ≥3 NRS units</td>
<td>84.3</td>
<td>71.6</td>
<td>12.7</td>
<td>0.08 to 24.7</td>
</tr>
<tr>
<td><strong>Patients with 1 dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in NRS score</td>
<td>6.1</td>
<td>4.5</td>
<td>1.6</td>
<td>0.69 to 2.4</td>
</tr>
<tr>
<td>Percentage decrease ≥3 NRS units</td>
<td>89.0</td>
<td>74.8</td>
<td>14.2</td>
<td>2.9 to 24.9</td>
</tr>
<tr>
<td><strong>Patients with ≥2 doses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in NRS score</td>
<td>4.0</td>
<td>4.3</td>
<td>-0.3</td>
<td>-2.3 to 1.7</td>
</tr>
<tr>
<td>Percentage decrease ≥3 NRS units</td>
<td>69.2</td>
<td>72.7</td>
<td>-3.5</td>
<td>-29.5 to 29.1</td>
</tr>
</tbody>
</table>

NRS, Numeric rating scale.

*Adjusted for location of pain and initial NRS score

†Includes 1 patient who received 3 doses.

### Table 3. Adverse effects of 1+1 hydromorphone patient-driven protocol versus physician-driven pain management.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>1+1 Patient-Driven Group n/N/%</th>
<th>Physician-Driven Group n/N/%</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90%</td>
<td>0/108/0.0</td>
<td>2/110/1.8</td>
<td>-1.8 (-6.4 to 1.9)</td>
</tr>
<tr>
<td>90–94%</td>
<td>5/108/4.6</td>
<td>2/110/1.8</td>
<td>2.8 (-2.5 to 8.7)</td>
</tr>
<tr>
<td>Pulse rate &lt;60 beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/106/3.8</td>
<td>9/106/8.5</td>
<td>-4.7 (-11.9 to 2.1)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/108/1.8</td>
<td>3/108/2.8</td>
<td>1.0 (-6.2 to 4.1)</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &lt;12 breaths/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/108/0.9</td>
<td>1/110/0.9</td>
<td>0.0 (-4.1 to 4.2)</td>
<td></td>
</tr>
<tr>
<td>Nausea†</td>
<td>11/64/17.2</td>
<td>8/66/12.1</td>
<td>5.1 (-2.9 to 13.0)</td>
</tr>
<tr>
<td>Vomiting†</td>
<td>3/64/4.7</td>
<td>1/56/1.8</td>
<td>1.9 (-4.5 to 8.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7/108/6.5</td>
<td>4/110/3.6</td>
<td>2.9 (-0.7 to 6.4)</td>
</tr>
</tbody>
</table>

*P=.71 data collapsed into oxygen saturation ≥95% and <95%.

†Denominators exclude patients who were nauseated or had vomited before administration of the first dose of IV opioid.

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control than physician-driven care, although the difference between the 2 groups of 1.1 numeric rating scale units did not meet our prespecified criterion for a minimal clinically significant change in pain of approximately 1.3 numeric rating scale units.15,18,24,25

The premise of the protocol was that a substantial protocolized initial dose of opioids (equivalent to 7 mg of morphine) would result in adequate initial control of pain among those who did not want more analgesia. We expected that the protocolized increase in dose after 15 minutes would lead to further decrease in pain among those who wanted more. The exploratory analyses demonstrated, not surprisingly, that the higher initial dose of morphine equivalents resulted in a greater decrease in pain than the lower initial dose of morphine equivalents in the physician-driven group. However, analyses showed that patients who wanted a second dose of hydromorphone did not experience as great a decrease in pain as patients who did not want more. We observed this same phenomenon in patients who received more analgesics in the physician-driven group. A possible explanation of this finding is that either the nature of the pain or a characteristic of these patients made it more difficult to control their pain, even with substantially higher doses of analgesics.

In this study, 32 patients in the 1 + 1 hydromorphone patient-driven group wanted more analgesics after 15 minutes. By the end of 60 minutes, only 7 patients who had received a second dose wanted more. Thus 101 (94%) of the patients entered into the 1 + 1 hydromorphone protocol achieved adequate pain control as determined by the patient declining further analgesia when asked. Because of the design of our trial, we could not determine the proportion of patients in the physician-driven group who achieved adequate pain relief.

It is widely recognized that there is large interindividual variability in the amount of opioids needed to control pain.1-3 Titration to effect with small boluses of opioid analgesic allows direct feedback from patients, indicating when adequate pain relief has been achieved. It also avoids overshooting the analgesic requirement of individual patients and allows patients to directly weigh adverse effects and analgesic effect of the administered agent to determine whether more pain medication is specifically needed for that individual. Although some have advocated nurse-initiated IV opioid titration,26-28 the ability to provide individualized titration of analgesia to effect is severely limited in the setting of increasingly crowded EDs, where pain management is only one of multiple urgent competing patient demands.

The 2-step 1 + 1 hydromorphone pain protocol we developed is an approximation of individualized titration of opioid in small boluses until pain is controlled, using a simplified, easily remembered strategy that rapidly leads to adequate (as defined by the patient) and safe analgesia. This simplification was made so that matching the amount of analgesic to the level of pain inherent in individualized titration could be undertaken more easily in EDs that are typically crowded and understaffed. A recent ED study has shown that administration of IV morphine in 2- to 3-mg boluses every 5 minutes was safe and effective in decreasing visual analog scale scores to 30 mm or below on a 100-mm scale for 82% of the patients.29 This was achieved with a median of 3 boluses; thus, nurses had to return 3 or more times for half the patients. The authors also report that there were protocol violations in the treatment of nearly half (44%) of the patients. This underscores the difficulty of following a time- and staff-intensive individualized titration protocol in the ED, where there are many competing demands placed on the clinical staff.

Hydromorphone may be the ideal IV opioid to use in the ED because it is approximately 7 times more potent and has a faster onset of action because of its increased lipophilia. However, as a recent Cochrane review concluded, there remain substantive gaps in our understanding of the efficacy and potency of hydromorphone that require further study.30

The incidence of adverse events and side effects was similar in the 2 groups (Table 3). The rate of desaturation in both groups was marginal and equivalent, with 5% experiencing oxygen desaturation less than 95% in the 1 + 1 hydromorphone patient-driven group versus 4% in the physician-driven group. All patients responded promptly to nasal cannula and needed no further intervention to maintain their oxygen saturation at 95% or higher.

Despite falling short of achieving clinical significance favoring the 1 + 1 protocol, this strategy is attractive because it is easier for the nursing staff: it requires no calculations (resulting in less opportunity for dosing error) and it uses amounts of hydromorphone consistent with how it is packaged (in either 1-mg or 2-mg vials).

In summary, the 2-step 1 + 1 hydromorphone protocol in which all patients receive 1 mg IV hydromorphone, followed by a second 1-mg IV hydromorphone bolus if requested 15 minutes later, resulted in adequate analgesia (as defined by the patient) by 60 minutes in 94% of patients. There were no between-group differences in incidence of side effects or adverse events, and no patient required use of naloxone. We conclude that the 1 + 1 hydromorphone patient-driven protocol is statistically superior and at least as clinically efficacious and safe as traditional physician-driven treatment of ED patients with acute severe pain.

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Author contributions: AKC, PEB, and EJG, conceived the study and designed the trial. AKC, PEB, and MD managed the data, including quality control. PEB analyzed the data and provided all figures and tables. AKC drafted the article, and all authors contributed substantially to its multiple revisions. AKC takes responsibility for the paper as a whole.

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REFERENCES

Legend: Higher numbers indicate greater decrease in pain scores. Negative numbers indicate increase in pain. Baseline is at the end of the initial bolus.

Figure E1. Distribution of Change in pain intensity scores by group.
Table E1. Distribution of initial dose and total dose of opioids in morphine equivalent units.

<table>
<thead>
<tr>
<th></th>
<th>1+1 Patient-Driven Group</th>
<th>Physician-Driven Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>N</td>
</tr>
<tr>
<td><strong>Distribution of first dose of opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
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<td>27</td>
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<tr>
<td><strong>Distribution of total dose of opioids</strong></td>
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