

# Efficacy of an Acute Pain Titration Protocol Driven by Patient Response to a Simple Query: Do You Want More Pain Medication?

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**Study objective:** We assess the efficacy of a simple pain titration protocol of 1-mg increments of intravenous hydromorphone, given at fixed intervals, driven solely by patient response to a yes/no question.

**Methods:** This was a prospective interventional cohort study of nonelderly adults with acute severe pain defined as requiring intravenous opioids in the judgment of the attending emergency physician. All patients received 1 mg intravenous hydromorphone and 30 minutes later were asked, "Do you want more pain medication?" Patients responding yes received an additional 1 mg of intravenous hydromorphone and were asked the same question 30 minutes after receiving it. Those responding no did not receive additional opioid and were asked the question again 30 minutes later. Each patient was queried 4 times. The primary endpoint was the proportion of patients achieving satisfactory pain control, defined as declining additional pain medication on 1 or more occasions.

**Results:** Of 215 patients enrolled, there were 8 protocol violations, leaving 207 patients with analyzable data; 205 of 207 patients (99%; 95% confidence interval 97% to 100%) achieved satisfactory analgesia at 1 or more points during the study. Nine patients desaturated below 95% on room air, 2 had respiratory rates less than 10 breaths/min, and 2 had pulse rates less than 50 beats/min. No adverse events were associated with amount of hydromorphone received.

**Conclusion:** A pain protocol, based on titration of 1 mg intravenous hydromorphone, driven solely by patient response to a simple standardized question repeated at intervals, resulted in achievement of satisfactory analgesia on at least 1 occasion in 99% of patients. [Ann Emerg Med. 2015;■:1-8.]

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### INTRODUCTION

#### Background

The amount of opioid needed to control pain is highly variable.<sup>1-4</sup> The recommended approach to address this inherent variability of response to opioids is to titrate to analgesic effect<sup>5-8</sup>; however, individual titration of opioids is highly resource intensive. A rough estimate of time needed for individual titration can be extrapolated from a postoperative titration study in which patients were given 2 to 3 mg of morphine every 5 minutes.<sup>9</sup> The median number of doses was 4, suggesting that adequate treatment of half of patients needing intravenous opioids would require more than 20 minutes. The conditions of emergency care in the United States are unlikely to provide a suitable environment for fully individualized treatment following a protocol based on 5-minute intervals.<sup>10</sup>

In recognition of the difficulty of providing individual titration to patients in many emergency departments (EDs), we developed a simplified pain protocol ("1+1" hydromorphone protocol) that addresses individual differences in response to opioids.<sup>11</sup> This protocol built in reassessment of need for additional analgesia at fixed intervals and specified a standard dose of a single intravenous opioid to be given at those times.<sup>12-14</sup> In this protocol, patients are asked the question "Do you want more pain medication?" 15 minutes after receiving the first 1-mg dose of intravenous hydromorphone. An affirmative response results in administration of an additional 1 mg of intravenous hydromorphone. A negative response results in no administration of pain medication at that time.

This earlier work allowed 1 additional dose of intravenous hydromorphone. The current study is an extension of this earlier work such that patients are

**Editor's Capsule Summary***What is already known on this topic*

Many emergency departments (EDs) use pain scoring to guide opioid analgesia.

*What question this study addressed*

How effective is analgesia instead directed by the repeated question "Do you want more pain medication"?

*What this study adds to our knowledge*

In this study of 207 ED adults administered repeated hydromorphone doses guided by patient request, essentially all (99%) achieved sufficient analgesia such that they declined further doses, including many with higher pain scores.

*How this is relevant to clinical practice*

Opioid analgesia is highly effective when directed by patient request, irrespective of pain scoring.

asked the same question repeatedly at approximately 30-minute intervals for the duration of the study, providing them the opportunity to obtain up to 4 mg intravenous hydromorphone in total, during a longer period of up to 4 hours. In essence, this is a "1+1+1+1" hydromorphone protocol.

**Importance**

The development of a simple, evidence-based protocol to treat acute pain holds the promise of safely providing adequate analgesia to patients over the full spectrum of opioid requirement through the use of a simple, easily remembered protocol.

**Goals of This Investigation**

The primary objective of this study was to determine the efficacy of a patient-driven pain titration protocol, which specifies a fixed quantity (1 mg) of a single opioid (hydromorphone), administered intravenously at fixed (approximately 30-minute) intervals, up to a maximum of 4 mg of intravenous hydromorphone during 4 hours, based entirely on the patient's yes/no response to a simple iterative question: Do you want more pain medication?

Because virtually all studies of pain protocols use quantitative measures of pain severity to assess efficacy, a secondary objective was to assess the concordance between the proportion of yes/no responses to the question "Do you want more pain medication?" and a commonly used

quantitative 0- to 10-point measure of pain severity, the numeric rating scale.

**MATERIALS AND METHODS****Study Design**

This was a prospective interventional cohort study of nonelderly adults (aged 21 to 64 years) presenting to the ED with acute pain of sufficient severity to require intravenous opioids in the judgment of the attending physician. All enrolled patients received an initial 1 mg of intravenous hydromorphone, followed by 0, 1, 2, or 3 additional 1-mg intravenous doses at approximately 30-minute intervals. Additional doses of hydromorphone were determined solely by patients' yes/no response to a single, scripted question: Do you want more pain medication? The study was approved by the institutional review board of the Montefiore Medical Center of the Albert Einstein College of Medicine.

**Setting**

The study took place in an inner-city teaching hospital ED with an annual census of more than 100,000 adults. The population is predominantly composed of underserved minorities.

**Selection of Participants**

Patients aged 21 to 64 years and presenting to the ED with acute pain of fewer than 7 days duration<sup>15</sup> were screened for enrollment.

Exclusion criteria were reported allergy to hydromorphone or morphine, systolic blood pressure less than 100 mm Hg, room air oxygen saturation less than 95% by pulse oximetry, respiratory rate less than 12 breaths/min, pulse rate less than 60 beats/min, alcohol or other drug intoxication, use of any opioids within the past 7 days, use of a monoamine oxidase inhibitor, weight less than 100 pounds, pregnancy, breast-feeding, or presence of any chronic pain syndrome, such as sickle cell disease or fibromyalgia.

Trained, experienced, full-time research associates fluent in English and Spanish obtained informed consent and enrolled patients referred to them by emergency physicians. Patients were recruited 24 hours a day, 7 days a week, from June 2013 to April 2014.

After providing written informed consent in English or Spanish, all patients received 1 mg intravenous hydromorphone. Thirty minutes later, each patient was asked, "Do you want more pain medication?" This same question was put to each patient 3 additional times. The response to each question determined the time elapsed until the question was asked again. If the patient declined

additional pain medication, that individual was asked the question 30 minutes later. If a patient responded affirmatively, that individual was asked whether he or she wanted additional pain medication again 30 minutes after receipt of the last dose of 1 mg intravenous hydromorphone.

When a patient responded yes to the standardized query, the research associate alerted the patient's physician, who ordered an additional 1 mg intravenous hydromorphone. The nurse then picked up the order, obtained the hydromorphone, and administered it. In accordance with previous data (unpublished), we anticipated that this process would take approximately 30 minutes. Thus, for patients who wanted more pain medication each time they were asked, the study period would be about 4 hours long, depending on the amount of time required to order, obtain, and administer each of the additional 1-mg increments of intravenous hydromorphone. In contrast, for patients who consistently responded negatively to the standard question each time they were asked, the study would be only 2 hours long. Thus, study duration ranged from 2 to 4 hours, depending on the patient's response to the standard question, which was asked of each patient on 4 occasions.

If patients wanted additional medication the final time they were asked, which was the point of study termination, the research associate notified the patient's attending physician, who provided subsequent pain management at his or her discretion.

Patients were also asked at the end of the study whether they were very satisfied, satisfied, unsatisfied, or very unsatisfied with treatment of their pain with this protocol.

## Methods of Measurement

Before patients received the first dose of opioid, research associates asked them to provide information on age, race or ethnicity, weight, nausea, vomiting, and location of pain. At each of 4 subsequent points, patients were asked, "Do you want more pain medication?" At these times, they were also asked to report their pain intensity on a standardized, valid, and reproducible 11-point numeric rating scale,<sup>16</sup> in addition to the presence of nausea, vomiting, or pruritus.

Oxygen saturation, respiratory rate, systolic blood pressure, and pulse rate were measured each time patients were asked whether they wanted more pain medicine and again at 15 minutes after receipt of each dose of intravenous hydromorphone. Adverse events were defined as oxygen saturation less than 95% on room air, systolic blood pressure less than 90 mm Hg, respiratory rate less than 10 breaths/min, pulse rate less than 50 beats/min, or use of naloxone at any time during or after the study.

## Data Collection and Processing

Data were collected on a hardcopy standardized data collection instrument. A trained data manager entered the data in SPSS Data Entry version 4.0 (SPSS, Inc., Chicago, IL) weekly. Double entry of the data set was performed independently by a second trained data manager. Discrepancies were reconciled by referral to the original data collection instrument. Ten percent of data collection instruments were then randomly selected for hand-auditing of data quality by the principal investigator.

## Primary Data Analysis

Descriptive statistics for the cohort are expressed as means with SDs, medians with interquartile ranges, or proportions (%), each as appropriate to data type and distribution. Inferential statistics are expressed as interval estimation with 95% confidence intervals (95% CIs).

The primary endpoint was the proportion of patients who achieved pain control at 1 or more points during the study, defined as declining the offer of an additional 1 mg of hydromorphone on at least 1 occasion. Secondary efficacy endpoints are reported as the proportion of patients receiving 1, 2, 3, or 4 mg total dose of hydromorphone during the course of the study. Safety endpoints are expressed as the proportion of adverse events and side effects. To assess the association between total dose of hydromorphone and frequency of adverse events, it was necessary to collapse the 4 hydromorphone dose categories into 2 (1 mg vs >1 mg) to avoid statistical distortion of data because of small expected cell sizes in the higher-dose categories.

To assess the concordance between patient response to the standardized query and numeric rating scale score, we calculated the mean pain score of patients who wanted and did not want additional opioid at each point and the 95% CI around the mean difference. We have also described the relationship between numeric rating scale pain scores and request for additional medication in a series of parallel coordinate line plots showing individual trajectories of pain scores for patients with different patterns of response to the standardized query. We used SPSS Statistics for Windows (version 22; SPSS, Armonk, NY) to perform statistical analyses and MedCalc (version 14; Ostend, Belgium) to produce the parallel coordinate line plots.

In accordance with our earlier studies,<sup>11,13,14</sup> we estimated conservatively that at least 75% of our cohort would achieve satisfactory analgesia, defined as refusing additional pain medication on 1 or more occasions when asked. We based the sample size on estimating 75% efficacy with a precision of  $\pm 5\%$ . We found that a sample size of 286 was needed to produce a 95% CI extending from 70% to 80%. We analyzed the data after 215 patients were

enrolled. We chose to stop early because the estimate of the primary outcome was substantially higher than expected and thus had tighter precision than initially required. PASS (version 12; PASS, Kaysville, UT) was used for the sample size calculation.

## RESULTS

We screened 696 patients. The most common reasons for exclusion were use of opioids within the past 7 days ( $n=109$ ), intravenous opioid not warranted in the judgment of the attending physician ( $n=69$ ), pain present for more than 7 days ( $n=69$ ), and presence of a chronic pain syndrome such as sickle cell disease ( $n=59$ ). We enrolled 215 patients, 8 of whom were excluded from further analysis because of protocol violations (1 for missing data and 7 for failure to receive intravenous hydromorphone after requesting it). Baseline features of the 207 members of the study cohort with analyzable data are shown in Table 1.

Two hundred five of 207 patients (99%; 95% CI 97% to 100%) achieved pain control on 1 or more occasions during the study period. The 2 patients who did not achieve this primary efficacy outcome received the maximum of 4 mg of hydromorphone and then requested additional medication 30 minutes after the last dose, at the study termination.

Of the 207 patients, 114 received 1 mg of hydromorphone (55%; 95% CI 48% to 62%), 78 received 2 mg (38%; 95% CI 31% to 44%), 9 received 3 mg (4%; 95% CI 2% to 8%),

**Table 1.** Baseline features of the study cohort.

Characteristic	N = 207
<b>Sex</b>	
Female, No. (%)	122 (59)
<b>Race/ethnicity, No. (%)</b>	
Hispanic	143 (69)
Black	44 (21)
White/other	20 (10)
<b>Age, mean (SD), y</b>	41 (12)
<b>Weight, mean (SD), lb</b>	177 (34)
<b>Location of pain, No. (%)</b>	
Abdomen/pelvis	153 (74)
Flank	22 (11)
Back	15 (7)
Extremities	8 (4)
Other	9 (4)
<b>Initial NRS pain intensity, No. (%)</b>	
5–7	21 (10)
8	27 (13)
9	41 (20)
10	118 (57)
<b>Nauseated or vomited before receiving first dose of opioid, No. (%)</b>	
Yes	134 (62)

NRS, Numeric rating scale.

and 6 received 4 mg (3%; 95% CI 1% to 6%). The 6 patients who received the maximum dose of 4 mg included 4 who declined additional medication the last time they were asked, thus achieving the efficacy outcome, plus the 2 patients recorded as having protocol failures who requested additional opioids after receiving the maximum dose. The median time from request for additional pain medication until receipt was 27 minutes (interquartile range 24 to 33 minutes).

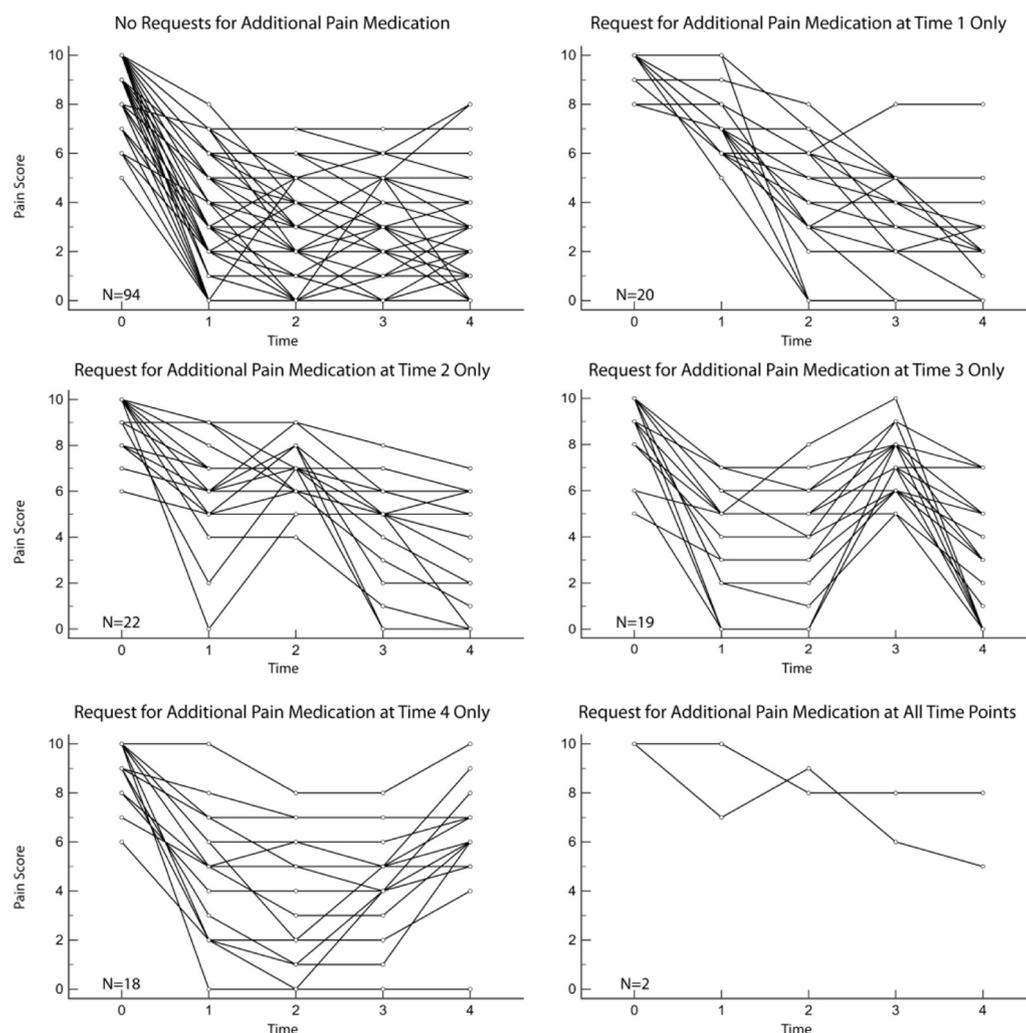
Table 2 shows the incidence of adverse events and side effects by total dose of hydromorphone received. Of the 9 patients who had transient oxygen desaturation less than 95% on room air, 2 desaturated below 90% (one to 85% and the other to 74%), both after their second dose of hydromorphone. All 9 patients returned promptly to an oxygen saturation greater than 95%, 5 after gentle arousal (they were sleeping) and 4 after receipt of 2 L oxygen by nasal cannula. No patients had apnea or required use of naloxone. The incidence of nausea was associated with dose of opioid, with 21% of patients (6/28) who received 1 mg hydromorphone reporting nausea versus 59% (19/32) who received 2 mg or more hydromorphone, for a difference of 38% (95% CI 13% to 57%). Forty-eight percent of patients received an antiemetic (ondansetron or metoclopramide), which was administered at the discretion of the treating physician.

The Figure shows the numeric rating scale scores of individual patients across the 5 points for 6 selected patterns of response to the question “Do you want more pain medication?” These patterns included patients who never requested additional pain medication, patients who requested additional medication at only 1 point (the first, second, third, or fourth time they were asked), and patients

**Table 2.** Adverse events and side effects by total amount of hydromorphone received.

Adverse Events and Side Effects	Total Amount of Intravenous Hydromorphone, mg			
	1	2	3	4
Number of subjects	114	78	9	6*
<b>Adverse events</b>				
Oxygen saturation <95%, No. (%)	3 (3)	5 (6)	1 (11)	0
RR <10/min, No. (%)	1 (1)	0	1 (11)	0
PR <50/min, No. (%)	1 (1)	1 (1)	0	0
SBP <90 mm Hg, No. (%)	1 (1)	0	0	0
<b>Side effects</b>				
Pruritus, No. (%)	8 (7)	8 (10)	2 (22)	2 (33)
Nausea, n/N (%) <sup>†</sup>	6/28 (21)	14/26 (54)	2/2 (100)	3/4 (75)
Vomiting, n/N (%) <sup>†</sup>	4/28 (14)	5/26 (19)	0/2	0/4

RR, Respiratory rate; PR, pulse rate; SBP, systolic blood pressure.  
 \*Of the 6 patients who received 4 mg intravenous hydromorphone, 4 said no and 2 said yes the final time they were asked. “Do you want more pain medication?”  
<sup>†</sup>Among patients who did not have nausea or vomiting before the study began.



**Figure.** Parallel line plots of selected patterns of individual numeric rating scale pain scores by time of patient request for additional analgesia. At time 0, all patients received the initial 1-mg intravenous hydromorphone. Time 1 is 30 minutes postbaseline. Subsequent points 2, 3, and 4 depend on individual patient response to the standardized question “Do you want more pain medication?” For patients responding negatively, the subsequent point represents 30 minutes after the patient was most recently asked. For patients responding affirmatively, the subsequent point represents 30 minutes after the patient received the most recent dose of intravenous hydromorphone. Individuals’ pain scores at each sequential point are connected by lines. Lines represent groups of individuals if more than 1 patient shares the same pattern of pain scores at any 2 sequential points.

who wanted additional pain medication at all times they were asked. The patients with these patterns of response represent 83% of the sample. The remaining 17% of patients had various patterns of requests for additional pain medications that were shared with 8 patients are less. The plots show the large variability in pain scores when patients requested and declined additional pain medication.

In aggregate, patients who requested more opioid had clinically and statistically higher mean pain intensity scores than those who did not at each point (Table 3). The mean pain score of patients when they requested additional opioid was approximately twice that of patients who did not want more. The range of pain scores when patients

wanted or did not want additional pain medication, also shown in Table 3, was wide.

Ninety-seven percent of patients were either very satisfied (67%) or satisfied (29%) with their pain treatment.

## LIMITATIONS

Because this study was designed to assess the efficacy of a protocol that allowed patients to receive up to 4 mg of hydromorphone during 4 hours, we chose to conduct a prospective interventional cohort study rather than a randomized controlled trial. Thus, the evidence provided here about efficacy is preliminary and requires further

**Table 3.** Number and proportion of patients responding to the standardized question “Do you want more pain medication?” at each point and mean pain score at that point.

Do You Want More Pain Medication?	N (%) <sup>*</sup>	Mean NRS Pain Score	Range of NRS Pain Scores	Difference in Mean NRS (95% CI)
<b>Time 1<sup>†</sup></b>				
Yes	42 (20)	7.4	3–10	3.6 (2.8–4.5)
No	165 (80)	3.8	0–10	
<b>Time 2<sup>‡</sup></b>				
Yes	41 (20)	7.2	4–10	4.3 (3.5–5.0)
No	166 (80)	2.9	0–7	
<b>Time 3<sup>‡</sup></b>				
Yes	31 (15)	7.1	3–10	4.0 (3.2–4.9)
No	176 (85)	3.1	0–10	
<b>Time 4<sup>‡</sup></b>				
Yes	38 (19)	6.8	0–10	4.4 (3.7–5.2)
No	167 (82)	2.4	0–8	

<sup>\*</sup>The number of patients who wanted or did not want additional medications at each point differs from that of patients shown in the Figure because the table displays data at each point, whereas the Figure shows selected patterns of response across all 5 points.

<sup>†</sup>Thirty minutes after the end of the first 1 mg of intravenous hydromorphone administered to all patients at the beginning of the study.

<sup>‡</sup>If patients answered no at previous points, they were asked the question again 30 minutes later. If patients answered yes at previous points, they were asked the question 30 minutes after receiving 1 mg intravenous hydromorphone.

critical examination, ideally in a randomized controlled trial setting. And although there were few adverse events, our study was not powered for safety outcomes.

We did not enroll the full sample that was initially targeted. Rather, we examined the data after 215 patients and found a much higher than anticipated proportion who achieved the primary endpoint, with substantially greater precision than was specified in the sample size estimate. Because this study was an exploratory cohort study and not a comparative clinical trial designed to test a hypothesis with a prespecified  $\Delta$ , the reduced sample size has no effect on either the accuracy or power of the analysis. Indeed, because the point estimate of 99% is so much farther out on the tail of the distribution than 75%, despite a smaller sample size, the precision of the estimate ( $\pm 2\%$ ) is tighter than that of the prespecified estimate (75%;  $\pm 5\%$ ) that we used to calculate the sample size.

This study was conducted in one of the busiest EDs in the country. The findings may not generalize to EDs with a lower volume of patients or higher staff-to-patient ratios. We found that approximately half of the patients did not receive additional pain medication within 30 minutes of the request. In better-staffed EDs, the regimen might deliver more timely care. In contrast, it is possible that care will be more delayed in settings similar to ours because the implementation of the clinical protocol was facilitated by research staff asking whether patients wanted more medication.

Our sample is drawn from a largely underserved urban Hispanic and black population, which has been traditionally understudied in the United States.<sup>17,18</sup> Whether these findings are generalizable to other racial or ethnic groups,

rural populations, or to individuals belonging to different socioeconomic strata cannot be determined from these data.

## DISCUSSION

In this prospective interventional cohort study, we wished to determine the efficacy of a simple, easily remembered ED pain titration protocol using a fixed dose (1 mg) of a single opioid (hydromorphone) up to a maximum of 4 mg, administered at regular intervals (30 minutes), based solely on the patient’s response to the query “Do you want more pain medication?” We found the protocol to be highly efficacious, with only 2 patients (1%) failing to achieve satisfactory pain relief on at least 1 occasion during the study period.

Although the study was not powered for safety outcomes, the protocol appears to be safe because there were few patients who desaturated below a clinically important threshold or had respiratory depression, bradycardia, or hypotension.

The low rate of most adverse events makes it difficult to assess whether there is a relationship with dose of hydromorphone. We did find that nausea, the most frequent side effect, increased significantly, from 21% to 59%, in patients who received 1 mg of hydromorphone and 2 or more mg of hydromorphone, respectively. The overall rate of nausea, even in patients who received only 1 mg of hydromorphone, was higher than that in other similar studies in the same population and may reflect sampling variability.<sup>11–14</sup> Previous work on the association between dose of opioid and frequency of nausea has been inconsistent. In 3 studies conducted at a single site, nausea was not significantly associated with total dose of

hydromorphone.<sup>12-14</sup> However, in 2 other studies, one at the same site<sup>11</sup> as the previous 3 and another in a postoperative setting,<sup>19</sup> an association did appear to be present. We made an effort to determine whether this variation might be accounted for by manufacturer, lot, or batch number of hydromorphone, but pharmacy records at this level of detail could not be obtained. Although there is a well-established association between nausea, vomiting, and opioid use, the strength of that association remains unclear.

Although there are numerous studies of specific analgesics for specific conditions (eg, sickle cell disease, migraine, and low back pain), there are few studies of acute treatment regimens that take into account variable analgesic requirement over a broad range of painful diseases and conditions. We sought to fill this gap by developing and testing several pain protocols during the last several years.<sup>11-14,20-22</sup> The core protocol specified administration of 1 mg intravenous hydromorphone to patients requiring intravenous opioids, followed by an optional second dose of 1 mg intravenous hydromorphone according to the patient's yes or no response to the same question (Do you want more pain medication?) used in the present study.<sup>11</sup> This original "1+1" hydromorphone protocol allowed 1 additional dose of pain medication to be administered. The present study is an extension of this previous work such that multiple additional doses of pain medication can be administered, to a maximum of 4 mg hydromorphone given in 1-mg increments during a maximum of 4 hours.

The decision to administer additional analgesic rests on reassessment of pain in the context of severity of opioid side effects. Because pain is a subjective perception, we reasoned that a therapeutic strategy, driven by a similarly subjective self-assessment of one's need for additional analgesia, might make clinical sense in determining how pain is treated. This represents a departure from more traditionally used determinants of need for analgesia, such as the 100-point visual analog scale, 11-point numeric rating scale, or clinical judgment.

Patients who wanted additional pain medication at each point had mean pain scores that were approximately twice as high as that of patients who did not want additional pain medication at each point. The strong concordance between the dichotomous measure and the numeric rating scale pain scores suggests that the simple binary scale and the more traditional 11-point integer numeric rating scale are measuring 2 closely related phenomena. Despite the clear relationship in the aggregate between mean numeric rating scale scores and request for additional pain medication shown in [Table 3](#), there was great variability in pain score at the times patients wanted and did not want additional pain medication, as shown in the [Figure](#). For

example, the pain scores of patients who never asked for additional pain medication the 4 times they were asked ranged from 0 to 8. When patients requested additional pain medication, the individual pain scores clearly increased for many patients but not all. The large variability of pain scores when patients requested and did not request additional pain medication shown in the [Figure](#) reinforces the necessity of asking patients whether they want additional medication rather than basing treatment decision on patients' reported level of pain.

We found that the simple dichotomous query at the center of this protocol appears to cross traditional barriers of communication, such as literacy, culture, educational level, and numeric ability. This is in contrast to the visual analog scale and numeric rating scale, which both require some facility with numbers and their interpretation. A non-numeric, yes or no question may be easier to comprehend among mildly confused patients, older adults, and those distracted by severe pain.<sup>23</sup> The standardized query also offers patients the opportunity to balance pain relief with the wide range of adverse opioid effects, including nausea, vomiting, pruritus, and a disconcerting sense of not being entirely in control of oneself. Finally, unlike the visual analog scale and numeric rating scale ratings of pain intensity, the question "Do you want more pain medicine?" that we repeatedly put to patients in this protocol immediately and unambiguously determines treatment, which is predetermined by protocol to be administration of 1 mg intravenous hydromorphone if patients answer yes. The choice of opioid, the amount given, the route of administration, and the intervals for reassessment and retreatment are all predetermined by protocol and driven by the patient's global self-assessment of pain severity, considered in the context of multiple other relevant variables, such as adverse effects, that may be of widely varying importance to individual patients.

We initially had concerns that a protocol in which patients could receive as much as 4 mg hydromorphone simply by requesting it when asked might facilitate drug-seeking behavior. However, we found no evidence to support this concern. Indeed, only 2 of 207 patients (1%) requested additional opioid at all points they were asked.

In summary, a patient-driven extended titration protocol composed of 30-minute-interval dosing of 1-mg increments of intravenous hydromorphone, determined solely by a patient's yes or no response to the simple query "Do you want more pain medication?" achieved pain control at some point during this 2- to 4-hour study in 99% of patients. Approximately half the patients required only 1 mg of hydromorphone (equivalent to approximately

7 mg morphine) to obtain pain relief. At the other end of the spectrum, given open access to as much as 4 mg of hydromorphone, only 1% of the cohort did not find that the protocol adequately controlled their pain.

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*Author contributions:* AKC, PEB, and EJG conceived the study and designed the trial. LH reviewed data collection instruments to ensure data quality and completeness. AKC and PEB analyzed the data and provided all figures and tables. AKC drafted the article, and all authors contributed substantially to its revisions. AKC takes responsibility for the paper as a whole.

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