JAMA Internal Medicine | Original Investigation

Association of an Opioid Standard of Practice Intervention With Intravenous Opioid Exposure in Hospitalized Patients

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IMPORTANCE Opioids are commonly used to treat pain in hospitalized patients; however, intravenous administration carries an increased risk of adverse effects compared with oral administration. The subcutaneous route is an effective method of opioid delivery with favorable pharmacokinetics.

OBJECTIVE To assess an intervention to reduce intravenous opioid use, total parenteral opioid exposure, and the rate of patients administered parenteral opioids.

DESIGN, SETTING, AND PARTICIPANTS A pilot study was conducted in an adult general medical unit in an urban academic medical center. Attending physicians, nurse practitioners, and physician assistants who prescribed drugs were the participants. Use of opioids was compared between a 6-month control period and 3 months following education for the prescribers on opioid routes of administration.

INTERVENTIONS Adoption of a local opioid standard of practice, preferring the oral and subcutaneous routes over intravenous administration, and education for prescribers and nursing staff on awareness of the subcutaneous route was implemented.

MAIN OUTCOMES AND MEASURES The primary outcome was a reduction in intravenous doses administered per patient-day. Secondary measures included total parenteral and overall opioid doses per patient-day, parenteral and overall opioid exposure per patient-day, and daily rate of patients receiving parenteral opioids. Pain scores were measured on a standard 0- to 10-point Likert scale over the first 5 days of hospitalization.

RESULTS The control period included 4500 patient-days, and the intervention period included 2459 patient-days. Of 127 patients in the intervention group, 59 (46.5%) were men; mean (SD) age was 57.6 (18.5) years. Intravenous opioid doses were reduced by 84% (0.06 vs 0.39 doses per patient-day, $P < .001$), and doses of all parenteral opioids were reduced by 55% (0.18 vs 0.39 doses per patient-day, $P < .001$). In addition, mean (SD) daily parenteral opioid exposure decreased by 49% (2.88 [0.72] vs 5.67 [1.14] morphine-milligram equivalents [MMEs] per patient-day). The daily rate of patients administered any parenteral opioid decreased by 57% (6% vs 14%; $P < .001$). Doses of opioids given by oral or parenteral route were reduced by 23% (0.73 vs 0.95 doses per patient-day, $P = .02$), and mean daily overall opioid exposure decreased by 31% (6.30 [4.12] vs 9.11 [7.34] MMEs per patient-day). For hospital days 1 through 3, there were no significant postintervention vs preintervention differences in mean reported pain score for patients receiving opioid therapy: day 1, −0.19 (95% CI, −0.94 to 0.56); day 2, −0.49 (95% CI, −1.01 to 0.03); and day 3, −0.54 (95% CI, −1.18 to 0.09). However, significant improvement was seen in the intervention group on days 4 (−1.07; 95% CI, −1.80 to −0.34) and 5 (−1.06; 95% CI, −1.84 to −0.27).

CONCLUSIONS AND RELEVANCE An intervention targeting the use of intravenous opioids may be associated with reduced opioid exposure while providing effective pain control to hospitalized adults.

JAMA Intern Med. 2018;178(6):759-763. doi:10.1001/jamainternmed.2018.1044
Published online May 14, 2018.

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Opioid medications are used widely for control of acute and chronic pain in hospitalized medical patients. While effective for analgesia, opioid administration via the intravenous route carries an increased risk of adverse effects, such as euphoria, nausea, and hypotension, compared with oral administration.[1] Furthermore, the intermittent, spiking pharmacokinetics of intravenous dosing are similar to the pattern known to drive the addiction process forward in animal models.[2] In the context of the current nationwide opioid crisis, significant efforts are under way to limit harm to patients by decreasing exposure to opioid medications; however, relatively little attention has been targeted to prescribing in the inpatient setting.

The subcutaneous route of administration is an established, effective method of opioid delivery with well-described and more favorable pharmacokinetics than the intravenous route. Subcutaneous injection of morphine demonstrates equivalent bioavailability while achieving a slightly delayed rise to maximum plasma concentration compared with intravenous administration.[3] Previous studies have demonstrated efficacy of subcutaneous opioids in controlling pain in a range of patient populations, including postsurgical patients[4] recovering from cardiac surgery,[5] cesarean delivery,[6] major gynecologic surgeries,[7] and pediatric surgery,[8] as well as patients with pain related to cancer.[9,10] A systematic review of 18 studies of various routes of opioid administration for control of cancer-related pain found no significant differences in efficacy or effectiveness compared with intravenous and subcutaneous routes.[1] We hypothesized that a 2-pronged approach of establishing a clinical practice standard and peer-to-peer education would reduce the use of intravenous opioids in favor of oral and subcutaneous opioid administration.

The objective of the intervention was a reduction in exposure to intravenous opioids in a population of adult medical inpatients. By educating medical staff about subcutaneous administration, we hoped to see uptake of this well-proven method of drug delivery and both fewer intravenous opioid exposure events (ie, doses) and lower overall exposure to opioids (ie, morphine-milligram equivalents [MMEs]). Pain scores were monitored to assess the effectiveness of analgesia.

Key Points

Question Can adopting a new standard of inpatient opioid prescribing that prefers oral and subcutaneous over intravenous administration result in reduced intravenous opioid exposure?

Findings In this pilot study of 127 patients and 2459 patient-days on an adult medical unit, intravenous opioid dosing was reduced by 84% after adopting an opioid standard of practice, with mean pain scores similar to those before implementation of the new standard.

Meaning This intervention may be associated with significant reduction in inpatient intravenous opioid exposure in adult medical patients; further investigation is warranted.

Methods

This study was conducted on a 28-bed general adult medical inpatient unit in a large academic medical center. Prescribing medical staff included associates of a 165-member team of hospital-employed internal medicine attending physicians, nurse practitioners, and physician assistants. Six varying prescribers (3 physicians and 3 nurse practitioners and/or physician assistants) were caring for unit patients on each day of the control and intervention periods, and prescribers rotated through the unit in 3- to 7-day blocks according to a preestablished, unrelated scheduling system. Unit staff included 5 to 6 nurses per shift, with staff varying throughout the study period. A 3-month intervention period was established a priori and compared with a 6-month historical control period. This initiative met the Yale University Human Investigation Committee criteria to be considered a quality improvement project; need for patient consent was waived.

All patients present for at least 1 midnight on the intervention unit were included in the analysis, and only opioid doses dispensed on the intervention unit were included. Patient-days that included the administration of a parenteral opioid were separated as parenteral opioid patient-days for the purposes of subgroup analysis. Parenteral doses of morphine and hydromorphone, which are the preferred formulary agents for parenteral opioid therapy at the institution, and oral doses of morphine, hydromorphone, oxycodone, and tramadol were included in the analysis. For the purpose of analyzing MMEs, a conversion factor of 1 was used to compare subcutaneous and intravenous routes.[3]

The electronic health record (Epic Hyperspace; Epic Systems Corp) was used as the primary data source; all prescribing information, dose administration information, and pain score entries were electronically captured as part of routine workflow. Pain scores were measured on a standard 0- to 10-point Likert scale (10 representing the worst pain), with nursing staff collecting patient-reported scores per routine hospital protocol.

Intervention

The intervention consisted of 2 elements: the adoption of a local opioid standard of practice for the unit and associated education for medical and nursing staff. The opioid standard of practice established the oral route of administration as preferred when patients were able to tolerate oral intake of any kind and established the subcutaneous route as preferred whenever parenteral opioids were required. Prescribing was not formally restricted; thus, the intravenous route remained available to prescribers throughout the intervention period. The standard of practice was developed and deployed jointly by physician (A.L.A.), physician assistant (S.M.M.), and nursing (D.L.D., C.L.H.) unit leadership.

Education was implemented for prescribers and nursing staff, targeting awareness of the subcutaneous route of opioid administration and the new local opioid standard of practice, as well as reviewing opioid equianalgesic conversion principles and basic pharmacokinetics. At the start of the 3-month

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intervention period, study investigators provided prescribers a 30-minute formal didactic presentation on these principles with the opportunity for questions and answers, as well as similar information via email. Follow-up email reminders were sent to prescribers at the 2- and 4-week marks. As part of a preexisting, twice-daily nursing "huddle," reminders and reinforcement were provided by nursing leadership to the unit nursing staff for 2 weeks prior to the formal introduction of the new standard of practice on the unit. Nurses were empowered to remind prescribers about the new standard.

Outcome Measures

The primary outcome was the number of intravenous opioid doses administered to the general inpatient population per patient-day. Secondary outcomes included total parenteral (intravenous and subcutaneous) doses administered per patient-day, the daily rate of patients on the unit administered any parenteral opioid, parenteral and overall opioid doses administered per patient-day, parenteral and overall opioid dosage administered in MMEs per patient-day,[11] and patients' mean reported pain score over each of the first 5 days of hospitalization.

Statistical Analysis

Statistical testing was performed using χ^2 analysis for categorical data; 2-tailed, unpaired *t* test for continuous data; and mixed-effects regression modeling to adjust for clustering of observations (Microsoft Excel, Microsoft Corp; RStudio). Findings were considered significant at $P < .05$.

Results

The 6-month control period and 3-month intervention period included 4500 patient-days and 2459 patient-days, respectively. Patients were similar between groups with respect to age, sex, body mass index, race, and primary discharge diagnosis category (**Table**). During the intervention, 65% of parenteral opioid doses were administered via the subcutaneous route compared with less than 1% during the control period.

Among the general patient population, intravenous opioid doses were reduced by 84% during the intervention period (0.06 vs 0.39 doses per patient-day, $P < .001$), and combined doses of parenteral opioids given by either intravenous or subcutaneous route were reduced by 55% (0.18 vs 0.39 doses per patient-day, $P < .001$) (**Figure 1**A). The daily rate of unit patients administered any parenteral opioid decreased by 57% during the intervention period (6% vs 14%, $P < .001$) period. In addition, the mean (SD) daily amount of parenteral opioids administered (measured in MMEs) decreased by 49% during the intervention period (2.88 [0.72] vs 5.67 [1.14] MMEs per patient-day) (Figure 1B). Doses of opioids given via either the oral or parenteral route were reduced by 23% during the intervention (0.73 vs 0.95 doses per patient-day, $P = .02$) (Figure 1C), and mean daily overall MME exposure decreased by 31% (6.30 [4.12] vs 9.11 [7.34] MMEs per patient-day) (Figure 1B). Mean pain scores were assessed for each patient receiving opioid therapy for the first 5 days of hospitalization. For hospital days 1 through 3, there were no significant differences in mean reported postintervention vs preintervention pain score (day 1: 5.62 vs 5.81; difference, -0.19; 95% CI, -0.94 to 0.56; $P = .62$; day 2: 4.79 vs 5.27; difference, -0.49; 95% CI, -1.01 to 0.03; $P = .07$; and day 3: 4.24 vs 4.78; difference, −0.54; 95% CI, -1.18 to 0.09; $P = .09$); however, significant improvement was seen in the intervention group on day 4 (3.75 vs 4.82; difference, −1.07; 95% CI, −1.80 to −0.34; $P = .004$) and day 5 (3.59 vs 4.65; difference, −1.06; 95% CI, −1.84 to −0.27; $P = .009$) (**Figure 2**).

Among the daily subset of patients receiving parenteral opioids, intravenous opioid doses were reduced by 62% during the intervention (1.03 vs 2.73 doses per parenteral-opioid patient-day, $P < .001$), while combined doses of parenteral opioids by either the intravenous or subcutaneous route did not differ significantly during the intervention (2.94 vs 2.82 doses per parenteral opioid patient-day, $P = .31$). The mean daily amount of parenteral opioids (measured in MMEs) administered on days that patients received any parenteral opioid increased by 17% during the intervention (46.17 [69.98] vs 39.51 [22.63] MMEs per parenteral opioid patient-day).

Table. Patient Characteristics

Characteristic	No. (%)		*P* Value[a]
	Control	Intervention	
No. of patients	287	127	
Age, mean (SD), y	56.1 (18.5)	57.6 (18.5)	.45
Men	113 (39.4)	59 (46.5)	.18
BMI	28.5 (8.9)	28.7 (8.9)	.81
Race (self-reported)			
White	191 (66.6)	86 (67.7)	.26
Black	66 (23.0)	23 (18.1)	
Asian	1 (0.3)	2 (1.6)	
Other	26 (9.1)	16 (12.6)	
Refused	3 (1.0)	0	
Primary discharge diagnosis category, %[b]			
Cardiac	21 (7.3)	12 (9.4)	.71
Endocrinologic	13 (4.5)	4 (3.1)	
Gastrointestinal	88 (30.7)	37 (29.1)	
Hematologic/oncologic	20 (7.0)	12 (9.4)	
Infectious	66 (23.0)	24 (18.9)	
Neurologic	18 (6.3)	6 (4.7)	
Ophthalmologic/ otolaryngologic	7 (2.4)	3 (2.4)	
Orthopedic	18 (6.3)	10 (7.9)	
Pulmonary	17 (5.9)	9 (7.1)	
Renal	8 (2.8)	2 (1.6)	
Rheumatologic	2 (0.7)	1 (0.8)	
Urologic/gynecologic	5 (1.7)	7 (5.5)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] χ^2 Testing was used to analyze categorical data; *t* testing was used for continuous data.

[b] Data were missing on 4 patients in the control group.

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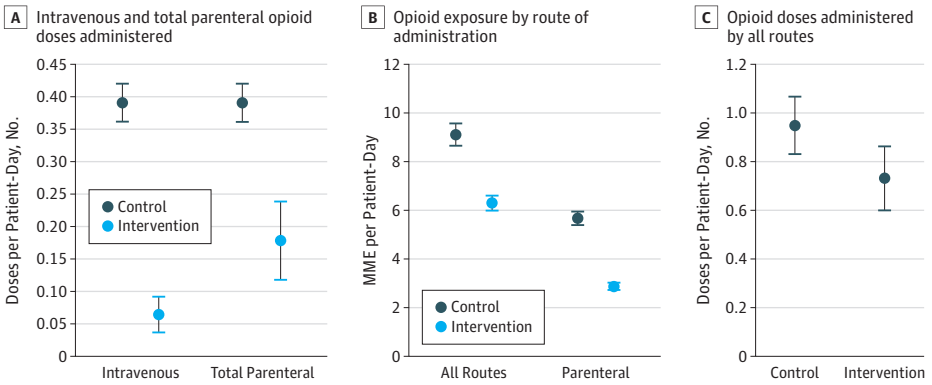
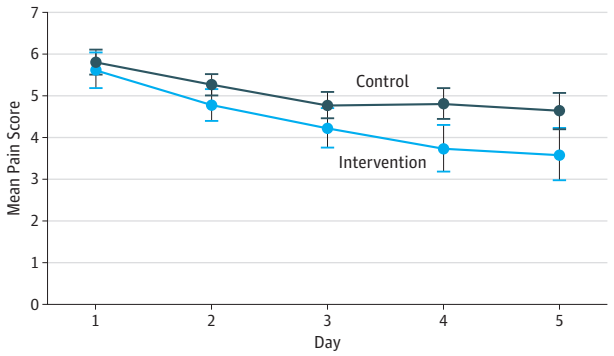
Figure 1. Parenteral, Intravenous, and Total Opioids Administered per Patient-Day



A, Total parenteral and intravenous opioid doses administered per patient-day. B, Mean amount of total opioids and parenteral opioids administered per patient-day. All opioid doses were converted to morphine-milligram equivalents (MMEs). C, Total opioid doses administered per patient-day. Whiskers indicate 95% CI.

Figure 2. Mean Daily Pain Score Reported by Patients Receiving Opioid Therapy During Each of the First 5 Days of Hospitalization



Higher score indicates more severe pain. Whiskers indicate 95% CI.

Discussion

Reducing iatrogenic harm from exposure to opioids is currently a focus of efforts across multiple medical specialties. With a recent study showing increased persistent opioid use after exposure in the perioperative setting,[12] hospital-associated opioid administration is an area deserving more attention. The literature does not currently include interventions specifically aiming to reduce the use of intravenous opioids by encouraging use of the equally efficacious and potentially less addicting subcutaneous route.

We designed a 2-part quality improvement initiative targeted to prescribers and nursing staff caring for patients on a 28-bed general adult medical unit. First, a local opioid standard of practice was established, with oral administration preferred for patients tolerating oral intake. If patients were unable to take pills, subcutaneous administration was preferred, although prescribers were not restricted in ordering any drug or route as part of this investigation. With targeted education, prescribers received information about the subcutaneous route and were made aware of the new local standard of practice; nursing staff were encouraged to actively question orders noted to be outside of the preferred standard.

Prescriber uptake of the subcutaneous route for parenteral administration was brisk, with 65% of parenteral doses given via subcutaneous injection during the intervention compared with minimal subcutaneous use during the control period. The daily rate of patients receiving parenteral opioids of any kind decreased by half; to some degree, this result reflects the preference for oral administration in appropriate patients. Significant reductions were observed in intravenous, parenteral (intravenous and subcutaneous), and combined oral and parenteral opioid doses administered during the intervention period. Similarly, overall patient exposure to both oral and parenteral opioids was significantly reduced when measured as MMEs. These results show that the intervention was associated with reduction in overall actual opioid exposure and that patients were not administered the same amount of parenteral opioid via a different route. At the same time, mean pain scores were similar or improved in the intervention group compared with the control group over the first 5 days of hospitalization.

While we hoped to see pain scores remain similar in the intervention group, an unexpected improvement was observed; there may be several explanations for this phenomenon. First, switching from intravenous to subcutaneous administration for parenteral opioids may have decreased exposure to the intermittent, spiking levels of drug and thereby decreased short-term dependence on the parenteral opioid for pain control. Switching from parenteral opioid administration to oral administration may have provided more long-acting, consistent pain control. Finally, an overall increase in awareness of opioid prescribing practices may have led to wider use of multimodal analgesic principles among prescribers and thereby less prescribing of opioids in general.

Limitations

To our knowledge, this is the first intervention of its kind in the literature. It was limited in that it was a pilot project conducted on a single adult inpatient medical unit in 1 academic medical center. Prescribers were all hospital-employed physicians and advanced practice clinicians, which likely helped to facilitate dissemination of education more quickly than in a setting in which several disparate groups of prescribers would be caring for patients. Prescribers in specialties other than internal medicine (ie, surgical specialties) were not involved in

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this study; whether it could be generalizable to other areas of practice has not yet been investigated. In addition, it is possible that any discomfort associated with subcutaneous opioid administration may not have been captured effectively by routine evaluation of pain scores.

These results occurred without any changes made to the electronic health record (ie, electronic decision support for opioid prescribing or changing electronic order entry default buttons away from automatically selecting the intravenous route for parenteral opioids). Changes such as these could potentially increase the outcome of the intervention further by supporting the new standard of practice. This intervention should be scalable to larger populations of inpatients, and future directions may include study in other areas of hospital practice, including the surgical, emergency, obstetric, pediatric, and critical care environments. This expansion could be facilitated by leveraging both additional peer-to-peer education across medical specialties as well as the electronic health record, providing real-time decision support along with central pharmacy monitoring of opioid prescribing. Several questions remain unanswered, such as whether adopting the new standard of practice can lead to decreased time from hospital admission to the transition from parenteral to oral opioids for acute pain and whether the intervention is associated with decreased length of stay, opioid-associated delirium, or the rate of patients discharged from the hospital with opioid prescriptions.

Conclusions

Adoption of a new standard of inpatient opioid prescribing, preferring the oral route of administration when available and the subcutaneous route when parenteral administration is required, coupled with education of prescribers and nursing staff, was associated with a reduction of inpatient exposure to intravenous opioids with improved pain control.

ARTICLE INFORMATION

Accepted for Publication: February 16, 2018.

Published Online: May 14, 2018. doi:10.1001/jamainternmed.2018.1044

Author Contributions: Dr Ackerman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ackerman, O'Connor, Doyle, Marranca, Haight, Fogerty.
Acquisition, analysis, or interpretation of data: Ackerman, O'Connor, Doyle, Marranca, Day, Fogerty.
Drafting of the manuscript: Ackerman, O'Connor, Doyle, Marranca, Haight, Fogerty.
Critical revision of the manuscript for important intellectual content: Ackerman, O'Connor, Doyle, Marranca, Day, Fogerty.
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Administrative, technical, or material support: Ackerman, Doyle, Marranca, Haight, Day.
Study supervision: Ackerman, O'Connor, Doyle, Haight, Fogerty.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Kayoko Shioda, DVM, MPH (Department of Epidemiology of Microbial Diseases, Yale School of Public Health), assisted with statistical analysis. There was no financial compensation.

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