Title
Hydromorphone Unit Dose Affects Intraoperative Dosing: An Observational Study.

Permalink
https://escholarship.org/uc/item/7xg442zb

Journal
Anesthesiology, 132(5)

ISSN
0003-3022

Authors
Ershoff, Brent D
Grogan, Tristan
Hong, Joe C
et al.

Publication Date
2020-05-01

DOI
10.1097/aln.0000000000003176

Peer reviewed

Hydromorphone Unit Dose Affects Intraoperative Dosing:

An Observational Study

Brent D. Ershoff, M.D.,

Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

Tristan Grogan, M.S.,

Department of Anesthesiology and Perioperative Medicine, Medicine Statistics Core, University of California, Los Angeles, Los Angeles, California.

Joe C. Hong, M.D.,

Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

Pamela A. Chia, M.D.,

Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

Eilon Gabel, M.D.,

Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

Maxime Cannesson, M.D., Ph.D.

Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California.

Abstract

Background: Although clinical factors related to intraoperative opioid administration have been described, there is little research evaluating whether administration is influenced by drug formulation and, specifically, the unit dose of the drug. The authors hypothesized that the unit dose of hydromorphone is an independent determinant of the quantity of hydromorphone administered to patients intraoperatively.

Address correspondence to Dr. Cannesson: 757 Westwood Plaza Suite 3325, Los Angeles, California 90095. mcannesson@mednet.ucla.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Methods: This observational cohort study included 15,010 patients who received intraoperative hydromorphone as part of an anesthetic at the University of California, Los Angeles hospitals from February 2016 to March 2018. Before July 2017, hydromorphone was available as a 2-mg unit dose. From July 1, 2017 to November 20, 2017, hydromorphone was only available in a 1-mg unit dose. On November 21, 2017, hydromorphone was reintroduced in the 2-mg unit dose. An interrupted time series analysis was performed using segmented Poisson regression with two change-points, the first representing the switch from a 2-mg to 1-mg unit dose, and the second representing the reintroduction of the 2-mg dose.

Results: The 2-mg to 1-mg unit dose change was associated with a 49% relative decrease in the probability of receiving a hydromorphone dose greater than 1 mg (risk ratio, 0.51; 95% CI, 0.40–0.66; $P < 0.0001$). The reintroduction of a 2-mg unit dose was associated with a 48% relative increase in the probability of administering a dose greater than 1 mg (risk ratio, 1.48; 95% CI, 1.11–1.98; $P = 0.008$).

Conclusions: This observational study using an interrupted time series analysis demonstrates that unit dose of hydromorphone (2 mg *vs.* 1 mg) is an independent determinant of the quantity of hydromorphone administered to patients in the intraoperative period.

Because opioids are frequently administered in the perioperative period, understanding factors that influence their dosing is of interest to the anesthesia provider and relevant to patient care. Whereas the effect of clinical based factors (such as weight,[1] sex,[2] history of opioid dependence[3]), and physician behavior[4] on perioperative opioid administration has been elucidated, the effect of nonclinical factors such as the manner in which opioids are packaged, formulated, and presented to the anesthesia provider is relatively obscure. The term "rational use" has been coined to explain the condition whereby medications are administered appropriately, taking into consideration a patient's needs and medical situation.[5] When patients are not given appropriate doses of medications based on their individual needs, the prescribing practice is considered irrational.

To date, there has been little research evaluating how opioid administration is influenced by its formulation and its unit dose in the perioperative period. Although this effect has been evaluated in a small retrospective study,[6] the effect of opioid unit dose on intraoperative opioid administration has not been definitively studied. At the University of California, Los Angeles, hydromorphone was historically dispensed to anesthesia providers in 2-mg vials. In July 2017, as a result of a change in the pharmaceutical supplier, hydromorphone became solely available in 1-mg vials. In a retrospective cohort study including more than fifteen thousand patients, we employed an interrupted time series analysis to test the hypothesis that the change in the unit dose of hydromorphone from 2 mg to 1 mg led to a decrease in the quantity of hydromorphone administered to patients in the intraoperative period.

Materials and Methods

Data Extraction

This study qualified for Institutional Review Board (IRB) exception status by virtue of having no direct patient contact and using a deidentified dataset (IRB No. 15–000518). The data were attained *via* our previously published perioperative data warehouse.[7] The

perioperative data warehouse is a structured reporting schema that contains a vast amount of clinical data, including medication administration, that were entered into the institution's electronic medical record. More specifically, the data originates from Clarity, the relational database created by EPIC (EPIC, USA) for data analytics and reporting. Only the patients who received hydromorphone during their anesthesia care and had their recovery in the postanesthesia care unit (PACU) were included in the analysis. Data were extracted from February 18, 2016, which was 500 days before the hydromorphone unit dose change from 2 mg to 1 mg, until March 9, 2018, the day on which the data extraction was performed. Total intraoperative hydromorphone doses were calculated from the anesthesia start-time to the anesthesia end-time according to the anesthetic record.

Study Design

In this observational cohort study, we used an interrupted time series analysis to test the hypothesis that the unit dose of hydromorphone was associated with its intraoperative dosing. We defined the unit dose as the dose of hydromorphone, in milligrams, contained in a single vial. The dispensing of hydromorphone was performed electronically *via* Pyxis Anesthesia Medstations (CareFusion Corporation, USA) which were present in each anesthetizing location, and not at a central location. Pyxis Medstations use single-dose mini-drawer pockets for the management of controlled substances, where each pocket only stores, and thus dispenses, a single ampule of hydromorphone. The anesthesia provider could choose what percent of the unit dose to administer to the patient; additional hydromorphone beyond that contained in a unit dose could be administered by dispensing an additional unit dose. For example, if a provider dispensed a 2-mg vial and wished to administer 2.4 mg of hydromorphone, a second 2-mg vial would need to be dispensed, and 1.6 mg of hydromorphone would be returned at the end of the case.

The study sample included 15,010 adult patients who received intraoperative hydromorphone as part of an anesthetic during the study period. Patients less than 18 yr of age were excluded. Before July 1, 2017 (n = 10,598), hydromorphone was only dispensed to anesthesia providers in 2-mg vials (cohort 1). The dose of hydromorphone administered was at the discretion of the anesthesia provider. Any remaining hydromorphone was returned to pharmacy per our controlled substance reconciliation policy. On July 1, 2017, the 2-mg hydromorphone unit dose was removed from inventory and was replaced by 1-mg hydromorphone vials (cohort 2). The change in the hydromorphone unit dose from 2 mg to 1 mg was attributable to changes in the pharmaceutical supplier, and was unrelated to any other policy changes in the operating rooms at that time. From July 1, 2017 to November 20, 2017 (n = 2,981), hydromorphone was only available in this 1-mg unit dose. In a similar manner, from November 21, 2017 until March 9, 2018 (n = 1,431), hydromorphone was reintroduced in the original 2-mg unit dose (cohort 3), with the 1-mg vial completely removed from inventory. Cases performed between July 1 and July 10 were excluded from the analysis to ensure that cohort 1 (hydromorphone 2-mg presentation) did not inadvertently cross over to cohort 2. An appropriate statistical method to analyze interrupted time series data is segmented regression, which allows the formal assessment, in statistical terms, of the impact of an intervention on the outcome of interest.[8] This includes

quantification and statistical testing of both immediate impacts (at the time of the change), as well as comparing longer term changes (slopes) before and after the change.

Statistical Analysis

Patient characteristics and study variables were summarized across cohorts using means ± SD and frequencies (%) unless otherwise noted. Characteristics were formally compared across cohorts by using one-way ANOVA and the chi-square test for continuous and categorical outcomes, respectively. To assess the impact of the change in hydromorphone unit dose on outcome measures, an interrupted time series analysis was carried out using the methodology described by Wagner.[8] Briefly, segmented regression models were built with change-points that represented the switch in hydromorphone unit dose. Specifically, the first change-point indicates the change in hydromorphone unit dose from 2 mg to 1 mg, whereas the second change-point indicates the reversion in hydromorphone unit dose from 1 mg to 2 mg. Segmented regression analysis allows the regression equation to be piecewise linear (*i.e.*, made of straight lines connected at the change points). Therefore, although the regression function is continuous, its first derivative is discontinuous. Linear regression was used to model continuous outcome and Poisson regression with robust standard error estimates were used to model binary outcomes.[9] When the outcome of interest is greater than 10%, the odds ratio derived from logistic regression no longer approximates the risk ratio,[10] and as such, Poisson regression was selected where the exponent-tiated coefficients from the Poisson regression model provide risk ratio estimates which offer a more interpretable effect size estimate. Predictors included time (in weeks) and terms for the slope in the preintervention period, the immediate intervention effect indicator, and the slope after the intervention. Time (in weeks) was assessed in the models in units of 10 to ease interpretation. Because models contained more than one change-point, separate terms for the immediate intervention effect indicator and postintervention slope were included for each change-point. Covariates included in the model are described below. To generate the predicted values displayed in the figures, individual predictions for each patient were computed using the multivariable segmented regression model and then aggregated at the weekly level. To test for the presence of auto-correlation in the time series analyses, we tested up to a 13-week (quarterly) lag, and by examining the Durbin-Watson statistics as well as autocorrelation function and partial autocorrelation function plots, found no evidence of autocorrelation within any of the models. Residual plot analyses did not reveal any obvious departures from normality, nonlinearity, or evidence of heteroscedasticity. No statistical power calculation was conducted before the study, and the sample size was based on all available data. All hypothesis tests were two-tailed with *P* values less than 0.05 considered statistically significant. Statistical analyses were performed using IBM SPSS V25 (USA) and SAS V9.4 (SAS Institute, USA).

Outcomes

Primary Outcome.—The primary outcome was intraoperative hydromorphone dose administration. This variable was analyzed as a dichotomous outcome variable with a cut-point at 1 mg. That is, a value of 1 was assigned to cases where greater than 1 mg of hydromorphone was administered intraoperatively, and a value of 0 was assigned to cases where less than or equal to 1 mg of hydromorphone was administered. In sensitivity

analysis, intraoperative hydromorphone dose administration was analyzed as a continuous variable.

Secondary Outcomes.—As a secondary outcome, cumulative opioid administration doses throughout the duration of the PACU admission were measured by oral morphine milligram equivalents. Morphine milligram equivalents included both intravenous and oral opioid formulations. Additionally, the cumulative intraoperative oral morphine milligram equivalents, as well as the sum of morphine milligram equivalents for the intraoperative and PACU periods were measured. We specifically explored intraoperative fentanyl administration across the three cohorts as fentanyl was overwhelmingly the most common opioid administered along with hydromorphone in the sample. Morphine, methadone, and sufentanil were rarely administered intraoperatively (0.3%, 0.2%, and 0.01% of cases, respectively). Pain scores based on the visual analog scale were measured at both admission and discharge from the PACU and compared across the three cohorts.

Covariates

Several clinical and demographic covariates were considered for inclusion in the multivariable analysis. Table 1 reports summary statistics of the covariates across the three presentation dose cohorts. Preoperative variables included patient age, sex, weight, body mass index, and American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status (with one variable indicating the numeric component and another variable indicating the presence of the emergency modifier). Intraoperative covariates included case duration (defined as the difference of anesthesia end time and start time), an indicator for whether ketamine was given intraoperatively, and variables indicating whether acetaminophen or ketorolac were given intraoperatively or within four hours of anesthesia induction. Other covariates included the primary surgical subspecialty performing the procedure, as well as the anesthesia type (*i.e.*, general anesthesia, monitored anesthesia care, or regional). Because surgical subspecialty contained 25 levels, rather than creating 24 new binary categorical variables, we collapsed the 25 categories into three broader categories for the primary analysis (table 1). Group 0 includes cardiac surgical procedures, group 2 includes procedure categories that would not be expected to have high opioid requirements (*i.e.*, dentistry, hematology, pediatric transplant hepatology, ophthalmology, pediatric hematology, and radiology), and group 1 refers to all other surgical subspecialties. In sensitivity analysis, several additional variables were included as covariates in the regression models. Intraoperative opioids including morphine, fentanyl, alfentanil, and an indicator for whether remifentanil was administered were included as covariates. Preoperative gabapentin use (less than 3% incidence), intraoperative lidocaine infusion (less than 0.3% incidence), as well as surgical subspecialty (as a 25-level variable) were assessed in sensitivity analyses as well.

There were minimal missing data among the covariates with values for weight, body mass index, ASA classification, age, anesthesia type, and surgical subspecialty missing for 38 (0.3%), 111 (0.7%), 97 (0.6%), 97 (0.6%), 36 (0.2%), and 176 (1.2%) patients, respectively. Erroneous values based on clinician judgment were removed, including one for weight (value of 0), two for body mass index (values of 0 and 2,914), and three for hydromorphone

(values of 50, 50, and 11.2). The mechanism of missing data was assumed to be missing completely at random, and therefore a complete case analysis (N = 14,549) was performed which would not be expected to bias coefficient estimates.

Results

Table 1 displays the summary statistics for patient demographic and clinical variables across unit dose cohorts. With the exception of a difference in the numeric component of the ASA (table 1), there were no statistically significant differences among patient demographic and clinical characteristics across cohorts. The prevalence of acetaminophen and ketorolac administration differed across the three cohorts with increased use of these nonopioid analgesics over time at our center.

Primary Outcome: Intraoperative Hydromorphone Dose Administered

In a segmented Poisson regression model, the change in the hydromorphone unit dose from 2 mg to 1 mg was associated with a 49% relative decrease in the probability of receiving a hydromorphone dose greater than 1 mg (risk ratio, 0.51; 95% CI, 0.40–0.66; $P < 0.0001$). Figure 1 displays the proportion of patients, each week, who received a dose of hydromorphone greater than 1 mg (*blue line*) as well as the predicted proportion who received such a dose based on the regression model (*red line*). Before the first change in unit dose, there was a small decrease, for each 10-week period, in the probability of receiving a dose greater than 1 mg (risk ratio, 0.97; 95% CI, 0.96–0.99; $P = 0.002$). That is, in the 499 days before the first change-point, the probability of receiving a dose greater than 1 mg of hydromorphone had a 3% relative decrease, per 10-week period. In the weeks after the introduction of the 1-mg unit dose, there was no significant change in total dose administered (risk ratio, 1.08; 95% CI, 0.89–1.32; $P = 0.434$). Because the original 2-mg hydromorphone unit dose was reintroduced in November 2017, we were able to explore whether its return was associated with an increase in intraoperative hydromorphone administration. The reintroduction of the 2-mg unit dose, at change-point 2, was associated with a 48% relative increase (compared with the 1-mg cohort) in the probability of administering a dose greater than 1 mg (risk ratio, 1.48; 95% CI, 1.11–1.98; $P = 0.008$.) There was no significant difference in the dose administered over time between change-point 2 and the end of the study period (risk ratio, 1.02; 95% CI, 0.74–1.41; $P = 0.903$). Table 2 provides the effect estimates, CI, and P values for each of the variables in the model.

Sensitivity Analyses

In a sensitivity analysis where hydromorphone unit dose was treated as a continuous variable, there was a similar association between unit dose and the dose administered. Figure 2 displays the mean dose of hydromorphone administered intraoperatively each week (*blue line*) along with the predicted mean dose administered based on the linear regression models (*red line*). In a segmented linear regression model, the first change-point indicating the switch from a 2-mg to 1-mg unit dose was associated with a 0.11-mg decrease in the hydromorphone dose administered (95% CI, 0.06–0.16; $P < 0.0001$). The second change-point indicating the reintroduction of the 2-mg unit dose was association with a 0.09 mg increase in the hydromorphone dose administered (95% CI, 0.02–0.15; $P = 0.008$). Table 3

provides the effect estimates, CI, and *P* values for each of the variables in these models. Further sensitivity analyses were performed for all models whereby additional covariates including fentanyl, morphine, alfentanil, remifentanil, gabapentin, lidocaine infusions, and surgical subspecialty were added to the multivariable model. Regardless of whether the outcome was modeled as a continuous or dichotomous variable, including these covariates did not qualitatively affect the results.

Secondary Outcomes

PACU Opioid Administration.—Given that hydromorphone unit dose was associated with intraoperative administration, we assessed whether the change in unit dose was associated with PACU opioid administration. Figure 3 displays the mean morphine milligram equivalents administered in the PACU each week (*blue line*) along with the predicted mean morphine milligram equivalents based on the regression model (*red line*). A segmented linear regression model with two change points did not demonstrate evidence of an association between hydromorphone unit dose and PACU cumulative morphine milligram equivalents. Specifically, the switch in hydromorphone unit dose from 2 mg to 1 mg was not associated with an increase in PACU opioid administration (mean difference, 1.55 mg; 95% CI, −0.33 to 3.43; *P* = 0.106). Similarly, there was no significant effect on PACU opioid administration following the reintroduction of the 2-mg unit dose (mean difference, 0.35 mg; 95% CI, −2.15 to 2.84 mg; *P* = 0.784). Table 4 provides the regression coefficients, CI, and *P* values for each of the variables in the model.

Intraoperative Fentanyl Administration.—Because fentanyl is the overwhelmingly the most common opioid administered intraoperatively along with hydromorphone at our institution, we explored whether the change in hydromorphone unit dose affected intraoperative fentanyl administration. In a segmented linear regression model there was no significant association between the unit dose and intraoperative fentanyl administration at both the first change point (mean difference, 0.56 mcg; 95% CI, −0.38 to 1.50; *P* = 0.245) as well as the second change point (mean difference, −1.02 mcg; 95% CI, −2.27 to 0.23; *P* = 0.111). Before the unit dose change, however, there was a 0.36-mcg, per 10-week, decrease in intraoperative fentanyl administration (95% CI, 0.26–0.46; *P* < 0.0001). Figure 4 displays the mean dose of fentanyl administered intraoperatively each week (*blue line*) along with the predicted mean dose administered based on the linear regression models (*red line*).

Associations between hydromorphone unit dose and additional secondary outcome variables including PACU pain scores, cumulative intraoperative morphine milligram equivalents, as well as the sum of intraoperative and PACU oral morphine milligram equivalents were similarly assessed using segmented regression models. For each model, the effect estimates for the change points were not significant. Table 5 provides summary statistics for all outcome measures across the three cohorts.

Discussion

In this retrospective observational study using an interrupted time series analysis, we show that the manner in which hydromorphone is presented to anesthesia providers (unit dose), influences their dosing administration practices. The change in unit dose from a 2-mg to a 1-

mg vial was associated with a significant decrease in intraoperative administration. The existence of this effect is further supported by the observation that the reintroduction of the 2-mg unit dose was associated with an increase in the intraoperative dose administered. Before the first unit dose change, there was evidence of a decrease in intraoperative hydromorphone administration over time. This decreasing of doses over time may be explained by an overall trend in providers trying to rely less on intraoperative opioids for analgesia as enhanced recovery after surgery programs were implemented.[4] The sudden decrease in hydromorphone administration corresponding to the introduction of the 1-mg hydromorphone unit dose is significantly greater than what would be expected by the overall trend. These results strongly suggest that clinicians' administration behavior is influenced not only by patient characteristics, but also by an extraneous environmental factor. After the first change point, the trend of decreased hydromorphone administration over time no longer persisted in the remainder of the study period. However, the effect estimates for the second and third cohorts were not statistically significant with wide CI, and therefore strong conclusions cannot be drawn about hydromorphone administration over time during these periods.

Given that the change in hydromorphone unit dose was attributable to a change in the pharmaceutical supplier and unrelated to any other policy changes, the study design approximates a natural experiment, whereby individuals are exposed to the intervention as a result of factors that are outside of the control of the investigator. This results in a design such that the mechanism governing exposure resembles random assignment and thus decreases the probability of unmeasured confounding. An interrupted time series analysis is an appropriate study design for a natural experiment whereby an intervention is introduced at a known point in time. A comparison of outcomes between exposures can be made while accounting for underlying trends in the outcome. The combination of an interrupted time series analysis design along with the underlying natural experiment design provides strong evidence that the effect of presentation dose on the dose administered is not due to confounding. Although it is theoretically possible that some other unknown change influencing administration behavior occurred coinciding with the introduction of the 1-mg presentation dose, we believe this is highly unlikely. Showing how the reintroduction of the 2-mg hydromorphone unit dose was associated with an increase in the intraoperative dose administered further strengthens the evidence for a causative association.

Given that hydromorphone unit dose was associated with the intraoperative dose administered, we examined whether there were corresponding changes with other metrics such as PACU opioid administration and pain scores. Specifically, we explored the hypothesis that the change in the unit dose from 2 mg to 1 mg would be associated with increased opioid administration in the PACU and increased pain scores. Interestingly, there was no evidence of an association between hydromorphone unit dose and any of the secondary outcomes, suggesting that although intraoperative hydromorphone administration decreased in response to a lower unit dose, it appears to have had a negligible effect on early postoperative pain and cumulative opioid administration. In another secondary analysis, we sought to determine whether the decrease in intraoperative opioid administration associated with the switch to a 1-mg unit dose was associated with an increase in intraoperative fentanyl administration. Although the quantity of fentanyl administration decreased over

time leading up to the hydromorphone unit dose change, the change in fentanyl administration associated with the switch in hydromorphone unit dose was not statistically significant. That is, there did not appear to be substitution of fentanyl in lieu of hydromorphone. The decrease in intraoperative administration over time may have been attributable to the general trend of increased use of multimodal analgesia and less reliance on intraoperative opioids.

Rosenfeld *et al.*[6] performed a retrospective study evaluating 100 patients undergoing robotically assisted laparoscopic radical prostatectomy, and found that a change in the presentation dose of fentanyl from a combination of 250 mcg and 100 mcg vials to solely a dose of 100 mcg led to a decrease in intraoperative fentanyl administration. One of the authors' cited limitations of this study was that it only included patients undergoing robotic assisted laparoscopic prostatectomies, and that it was a retrospective study in a limited number of patients and therefore was possibly con-founded. Given the recent trend in decreasing the reliance on intraoperative opioids, it is possible that the decrease in fentanyl in the pre and post group in their study was related to this trend and not the effect of the presentation dose. In fact, in their study, they found that there was a decrease in the intraoperative administration of other opioids even though those presentation doses did not change.

In the current study, by using an interrupted time series analysis with more than fifteen thousand patients, we provide strong evidence that the effect on intraoperative clinician dosing extends beyond a single class of drugs. There exist other studies evaluating how the introduction of drug formulations affect prescribing practices although these are limited to outside of the perioperative period. Gomes *et al.*, for example, performed a time series analysis whereby the effect of the introduction of OxyNeo (controlled release oxycodone) was associated with a significant reduction in the quantity of long-acting opioids dispensed. [11] They found that the introduction of OxyNeo was associated with a decrease in oxycodone prescriptions that was partially offset by an increase in hydromorphone prescriptions. There has been an increased focus on the effect of intraoperative opioid administration on adverse outcomes. Recently, Long *et al.* demonstrated that higher intraoperative opioid administration was associated with increased readmission rates.[12] As the adverse effects of intraoperative opioid administration become better elucidated, understanding factors that influence intraoperative dosing become important.

Although the nature of this study precludes a definitive determination as to the reason for the lower doses administered in the 1-mg unit dose cohorts, we propose one theory. At our institution, anesthesia providers are required to return unused drug to the pharmacy as hydromorphone is a controlled substance. When the dose administered equals the presentation dose, or a multiple thereof, the anesthesia provider does not need to return unused medication to the pharmacy, which thereby decreases time spent on documentation. Because hydromorphone is a controlled medication (Drug Enforcement Administration Schedule II in United States, Misuse of Drugs Act Class A in United Kingdom, and similarly controlled in majority of developed nations), our notion of minimizing waste documentation is widely applicable. With a decrease in the unit dose, a provider may be encouraged to decrease the amount of drug he or she would normally administer so that it

equals the unit dose, and thereby not have to return a portion of the additional 1-mg vial he would need to dispense. To explore this hypothesis, we examined the proportion of cases in which exactly 1 mg of drug was administered in the 2-mg *versus* the 1-mg cohorts. The proportion of cases in which exactly 1 mg of hydromorphone was administered was significantly higher in the 1-mg cohort compared with the 2-mg cohorts (10.9% *vs.* 19.3% *vs.* 13.8% for cohorts 1, 2, and 3, respectively; $P < 0.0001$). The fact that a significantly larger proportion of patients received 1 mg in the 1-mg cohort compared with the 2-mg cohort, but that so few received only a slightly higher dose of 1.2 mg in the 1-mg cohort, suggests there was a barrier to drawing up an additional vial.

Although the study was not designed to evaluate how such a phenomenon could be applied in a health care system to benefit patient care, it is clear that unit dose has the ability to influence administration behavior. This highlights the importance of choosing the unit dose of drugs for an anesthesia formulary. We considered whether the price of hydromorphone presentation may affect clinician administration practices. However, anesthesia providers were not offered information on the cost of the old *versus* the new hydromorphone presentation. Furthermore, the acquisition costs of both hydromorphone presentations were $1.28 *versus* $1.03 for the 2-mg *versus* 1-mg ampules, respectively. Thus, even if the anesthesia providers had sought out this information on their own, we do not believe cost considerations would have played a factor in their clinical decision making regarding drug administration.

Study Limitations

Because this study is an observational study, there exists the possibility that the presence of unaccounted confounding variables may be inducing the observed association between unit dose and the outcome variables. Given the interrupted time series study design, and the fact that the intervention, namely the unit dose changes, were unrelated to any other policy changes, the distribution of other variable, and therefore, possible confounding variables, would not be expected to differ across the study cohorts. If there existed other changes in variables that happened to coincide closely with the changes in hydromorphone unit dose, then this may partially invalidate the results. As mentioned above, however, this is unlikely given the fact that the effect was reversed with the reintroduction of the 2-mg hydromorphone unit dose in cohort 3. The duration of period 1 was substantially longer than that of periods two and three. The duration of period 2 was not under the control of the investigators because this was a natural experiment. It is possible that had the length of periods 2 and 3 been longer, we could have more care-fully studied the sustainability of the effect over time, and had more power to assess any changes in hydromorphone dosing over time in between the change points. Based on the design of the study, there was no expected selection bias nor was there measurement bias. This study is also unable to adequately address the dose response of this effect, that is, to what degree clinicians' behavior would change in response to a change in unit dose of a certain magnitude. Because this was a single-center study, we are unable to determine whether such an effect would be present in other environments.

In conclusion, this observational study using an interrupted time series analysis demonstrates that unit dose of hydromorphone (2 mg *vs.* 1 mg) is an independent determinant of the quantity of hydromorphone administered to patients in the intraoperative period.

Research Support

References

1. Ingrande J, Lemmens HJ: Dose adjustment of anaesthetics in the morbidly obese. Br J Anaesth 2010; 105 Suppl 1:i16–23 [PubMed: 21148651]

2. Zeidan A, Al-Temyatt S, Mowafi H, Ghattas T: Gender-related difference in postoperative pain after laparoscopic Roux-En-Y gastric bypass in morbidly obese patients. Obes Surg 2013; 23:1880–4 [PubMed: 23695438]

3. Lerchl-Wanie G, Angster R: [Perioperative analgesia for opioid tolerant patients]. Anaesthesist 2010; 59:657–70; quiz 671–2 [PubMed: 20625693]

4. Brandal D, Keller MS, Lee C, Grogan T, Fujimoto Y, Gricourt Y, Yamada T, Rahman S, Hofer I, Kazanjian K, Sack J, Mahajan A, Lin A, Cannesson M: Impact of enhanced recovery after surgery and opioid-free anesthesia on opioid prescriptions at discharge from the hospital: A historical-prospective study. Anesth Analg 2017; 125:1784–92 [PubMed: 29049123]

5. Ofori-Asenso R, Agyeman AA: Irrational use of medicines: A summary of key concepts. Pharmacy (Basel) 2016; 4

6. Rosenfeld DM K K, Spiro JA, Gorlin AW, Ramakrishna H, Trentman TL: The effect of ampule size of fentanyl on perioperative intravenous opioid dosing. J Anaesthesiol Clin Pharmacol 2018: 513–7 [PubMed: 30774233]

7. Hofer IS, Gabel E, Pfeffer M, Mahbouba M, Mahajan A: A systematic approach to creation of a perioperative data warehouse. Anesth Analg 2016; 122:1880–4 [PubMed: 27195633]

8. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D: Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002; 27:299–309 [PubMed: 12174032]

9. Zou G: A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004; 159:702–6 [PubMed: 15033648]

10. Zhang J, Yu KF: What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998; 280:1690–1 [PubMed: 9832001]

11. Gomes T, Mastorakos A, Paterson JM, Sketris I, Caetano P, Greaves S, Henry D, Canadian Network for Observational Drug Effect Studies I: Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone: A time series analysis. CMAJ Open 2017; 5:E800–7

12. Long DR, Lihn AL, Friedrich S, Scheffenbichler FT, Safavi KC, Burns SM, Schneider JC, Grabitz SD, Houle TT, Eikermann M: Association between intraoperative opioid administration and 30-day readmission: A pre-specified analysis of registry data from a healthcare network in New England. Br J Anaesth 2018; 120:1090–102 [PubMed: 29661386]

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Drug dosing during anesthesia should be determined by clinical factors

- To the extent that clinicians might consider the amount of drug in a single-patient-use vial to be a unit dose, the amount of drug in vials might influence use

What This Article Tells Us That Is New

- The investigators used a natural experiment in which their institution switched from 2-mg vials of hydromorphone to 1-mg vials, and then back to 2-mg vials

- Using a sophisticated segmented regression analysis, they show that patients were far more likely to be given 1 mg hydromorphone when smaller vials were provided

- The contents of single-patient-use vials influences drug use and might be used to guide practice
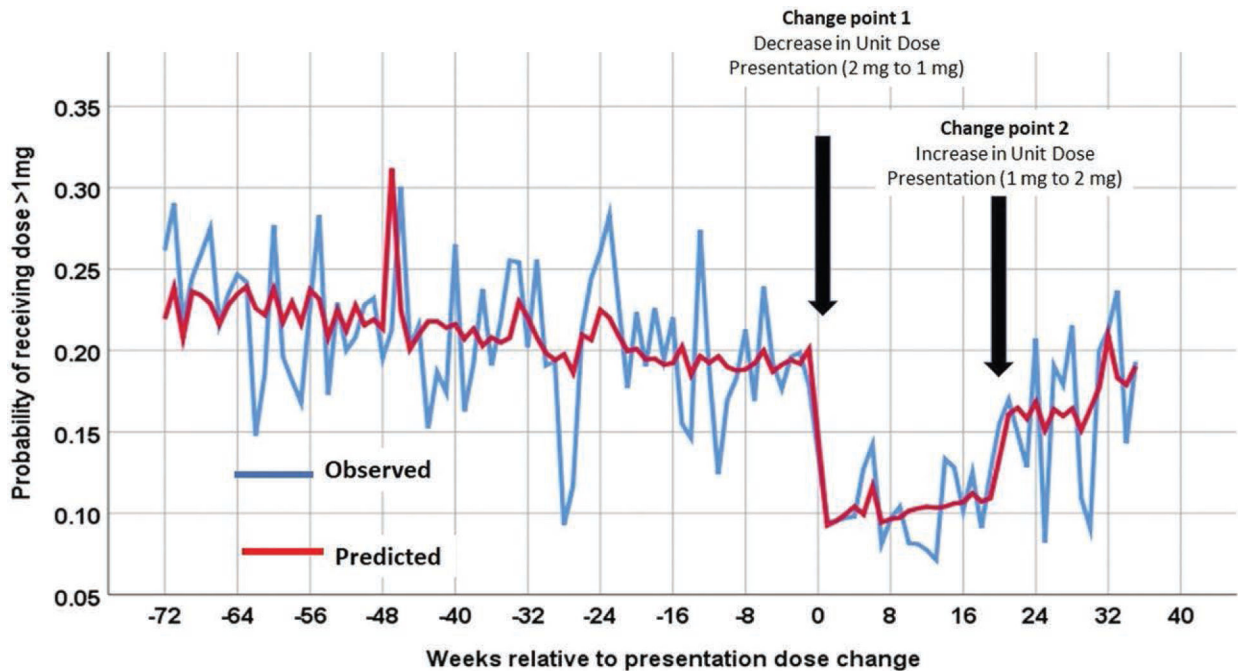
Fig. 1.

Interrupted time series analysis: hydromorphone unit dose presentation over time as a binary outcome. Plots of the time series analyses illustrating the proportion of patients, each week, who received a hydromorphone administration dose greater than 1 mg as a function of time. The *blue line* indicates the *observed* proportion of patients, whereas the *red line* indicates the *predicted* proportion based on the segmented regression model. To generate the predicted value, individual predictions for each patient were computed using the multivariable segmented regression model and then aggregated at the weekly level. Before the first change-point at week 0, there was a small decrease in the proportion of patients receiving a dose greater than 1 mg as a function of time. At the first change-point, indicating the switch from a 2-mg to a 1-mg unit dose presentation, there was a statistically significant decrease in the proportion of patients receiving a hydromorphone administration dose greater than 1 mg. At the second change-point (in week 20) indicating the switch from a 1-mg back to a 2-mg unit dose presentation, there was a statistically significant increase in the proportion of patients receiving a hydromorphone administration dose greater than 1 mg.
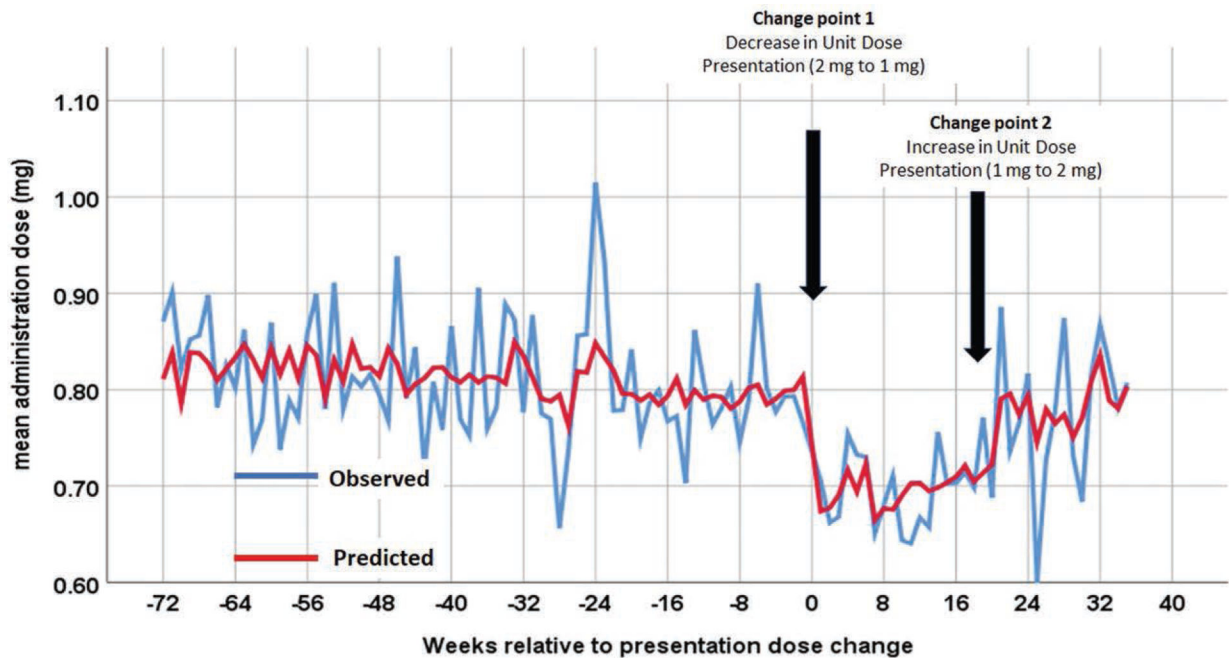
Fig. 2.
Interrupted time series analysis: hydromorphone unit dose presentation over time as a continuous outcome. A plot of the time series analysis illustrating the mean hydromorphone administration dose of hydromorphone, as a function of time (per week). The *blue line* indicates the *observed* mean administration dose within each week while the *red line* indicates the *predicted* mean administration dose within each week based on the segmented regression model. To generate the predicted value, individual predictions for each patient were computed using the multivariable segmented regression model and then aggregated at the weekly level. Before the first change-point at week 0, there was a small decrease in administration dose as a function of time. At the first change-point, indicating the switch from a 2-mg to à 1-mg unit dose presentation, there was a statistically significant decrease in the mean hydromorphone administration dose. At the second change-point (in week 20) indicating the switch from a 1 mg back to a 2-mg unit dose presentation, there was a significant increase in the mean administration dose of hydromorphone.
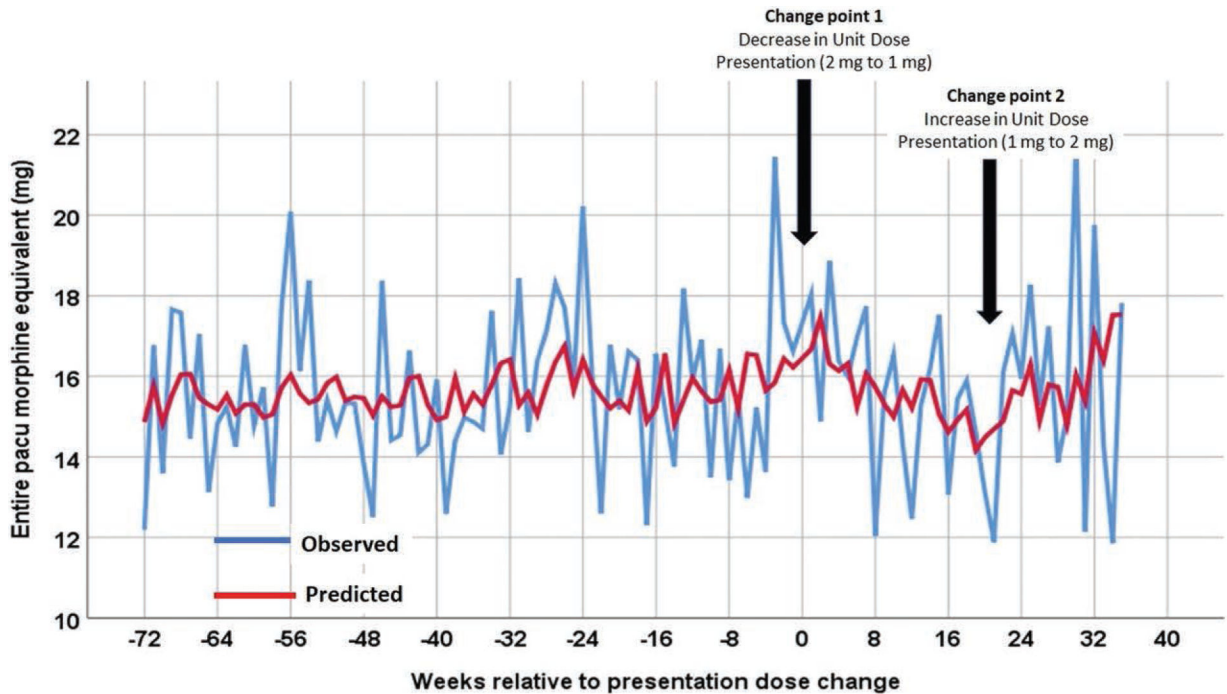
Fig. 3.
Interrupted time series analysis: postanesthesia care unit (PACU) opioid administration in morphine milligram equivalents over time. A plot of the time series illustrating the mean morphine milligram equivalents administered in the PACU as a function of time (per week). There was no significant difference in PACU opioid administration at any of the change points, indicating that hydromorphone unit dose did not have a significant effect on postoperative opioid consumption. The *blue line* indicates the *observed* proportion of patients, whereas the *red line* indicates the *predicted* proportion based on the segmented regression model. To generate the predicted value, individual predictions for each patient were computed using the multivariable segmented regression model and then aggregated at the weekly level.
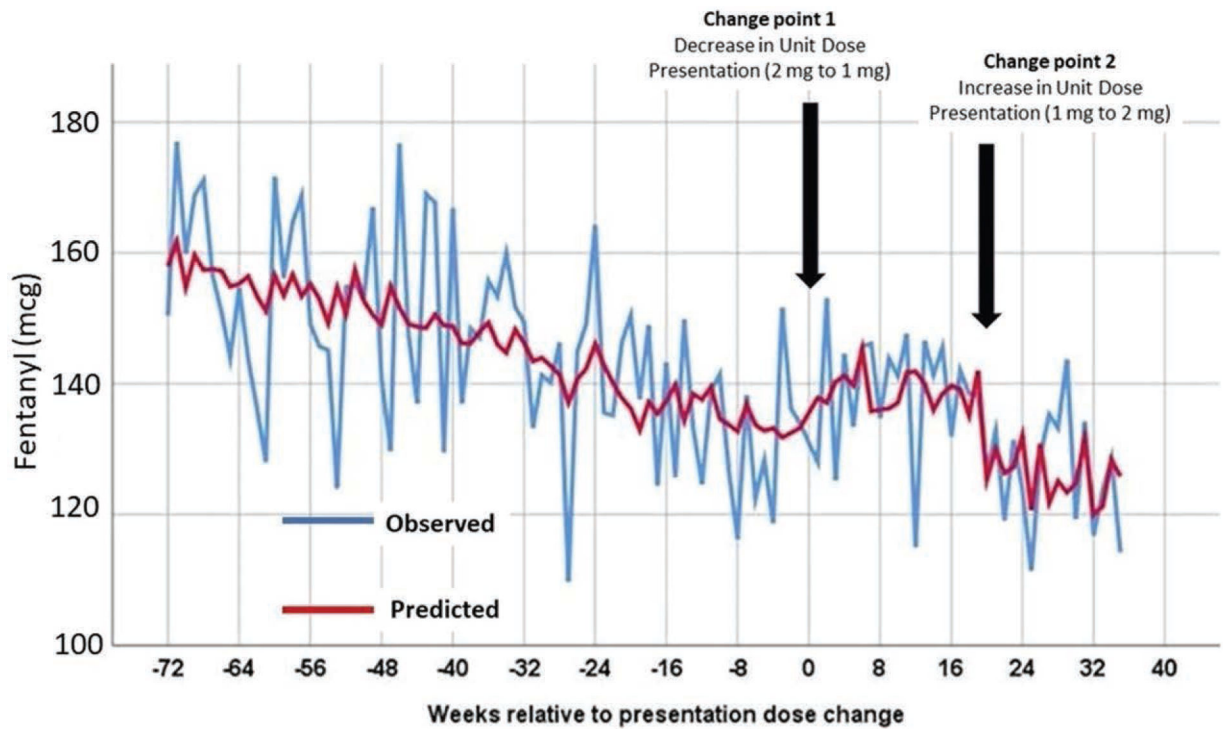
Fig. 4.
Interrupted time series analysis: intraoperative fentanyl administration over time. A plot of the time series analysis illustrating the mean intraoperative fentanyl administration dose as a function of time (per week). There was no significant difference in intraoperative fentanyl administration at any of the change points, indicating that hydromorphone unit dose did not have a significant effect on intraoperative fentanyl administration. Before the first change-point at week 0, however, there was a small decrease in administration dose as a function of time. The *blue line* indicates the *observed* mean administration dose within each week, whereas the *red line* indicates the *predicted* mean administration dose within each week based on the segmented regression model. To generate the predicted value, individual predictions for each patient were computed using the multivariable segmented regression model and then aggregated at the weekly level.

Table 1.

Clinical Characteristics of Patients across Cohorts

	Cohort 1 (n = 10,311)	Cohort 2 (n = 2,877)	Cohort 3 (n = 1,361)	P Value
ASA classification				0.005
I	1,122 (10.9%)	264 (9.2%)	152 (11.2%)	
II	4,845 (47.0%)	1,304 (45.3%)	589 (43.3%)	
III	4,157 (40.3%)	1,245 (43.3%)	587 (43.1%)	
IV	186 (1.8%)	63 (2.2%)	33 (2.4%)	
V	1 (< 0.1%)	1 (< 0.1%)	0 (0%)	
ASA(E)	366 (3.6%)	110 (3.8%)	36 (2.7%)	0.144
Sex, % male	4,718 (45.8%)	1,358 (47.2%)	654 (48.1%)	0.147
Weight , kg	79.0 ± 19.9	79.3 ± 20.2	78.5 ± 19.8	0.449
Ideal weight, kg	63.8 ± 10.7	63.9 ± 10.7	64.2 ± 10.9	0.346
Body mass index, kg/m^2	27.3 ± 6.2	27.5 ± 6.3	27.1 ± 6.1	0.165
Age, yr	51.9 ± 16.8	52.5 ± 16.6	51.7 ± 16.5	0.224
Ketamine	490 (4.8%)	146 (5.1%)	66 (4.9%)	0.774
Acetaminophen	6,942 (67.3%)	2,088 (72.6%)	1,014 (74.5%)	< 0.001
Ketorolac	692 (6.7%)	179 (6.2%)	118 (8.7%)	0.010
Remifentanil	979 (9.5%)	280 (9.7%)	129 (9.5%)	0.926
Alfentanil	214 (2.1%)	54 (1.9%)	24 (1.8%)	0.636
Anesthesia type				0.060
0	10,057 (97.5%)	2,804 (97.5%)	1,317 (96.8%)	
1	65 (0.6%)	25 (0.9%)	18 (1.3%)	
2	189 (1.8%)	48 (1.7%)	26 (1.9%)	
Subspecialty				0.259
0	10,110 (98.0%)	2,833 (98.5%)	1,333 (97.9%)	
1	34 (0.3%)	12 (0.4%)	7 (0.5%)	
2	167 (1.6%)	32 (1.1%)	21 (1.5%)	

Descriptive statistics of demographic and clinical characteristics are provided for patients stratified by cohort membership. Cohorts 1 and 3 refer to the time periods with a 2-mg unit dose presentation, and cohort 2 refers to the time period with a 1-mg unit dose presentation. Continuous variables are presented as mean ± SD, and categorical variables are presented as number (percentage). *P* values for the measure of association between the variable and cohort are provided. Comparisons for continuous variables were performed using the independent samples *t* test and comparisons for categorical variables were performed using the chi-square test. The variables "Ketamine," "Remifentanil," and "Alfentanil" indicate the proportion of cases in which these drugs were administered intraoperatively. The variable "Acetaminophen" and "Ketorolac" indicate the proportion of cases in which these drugs were administered intraoperatively. The variable "Anesthesia type" indicates the type of anesthesia administered to the patient (*i.e.*, general anesthesia [0], neuraxial anesthesia [1], or monitored anesthesia care [2]). The variable "Subspecialty" indicates

the surgical subspecialty group to which the patient belonged (see the Materials and Methods section for description). ASA, American Society of Anesthesiologists Physical Status; ASA(E), ASA Physical Status emergency indicator.

Table 2.

Risk Ratios with the Corresponding *P* Values and 95% CI for Predictors from the Hydromorphone Interrupted Time Series Analysis with a Binary Outcome

Predictor	Risk Ratio (95% CI)	*P* Value
Change (2 mg→1 mg)	0.51 (0.40–0.66)	< 0.0001
Change (1 mg →2 mg)	1.48 (1.11–1.98)	0.008
Prechange (2 mg→1 mg)	0.97 (0.96–0.99)	0.002
Postchange (2 mg→1 mg)	1.08 (0.89–1.32)	0.434
Postchange (1 mg→2 mg)	1.02 (0.74–1.41)	0.903
Weight, 10-kg	1.10 (1.05–1.15)	< 0.0001
Body mass index, kg/m^2	0.99 (0.97–1.00)	0.100
Age, 10-yr	0.87 (0.85–0.89)	< 0.0001
Sex, % male	0.98 (0.90–1.08)	0.745
ASA Classification	1.03 (0.98–1.09)	0.224
ASA(E)	0.64 (0.48–0.85)	0.002
Case duration, 60-min	1.10 (1.07–1.13)	< 0.0001
Ketamine	1.78 (1.59–2.00)	< 0.0001
Acetaminophen	0.88 (0.82–0.95)	0.001
Ketorolac	0.99 (0.85–1.15)	0.850
Subspecialty		< 0.0001
(0 *vs.* 2)	0.52 (0.42–0.64)	< 0.0001
(1 *vs.* 2)	0.58 (0.30–1.10)	0.093
Anesthesia type		0.005
(0 *vs.* 2)	0.73 (0.59–0.90)	0.003
(1 *vs.* 2)	0.47 (0.27–0.83)	0.009

This table displays the risk ratios, 95% CI, and *P* values for each of the variables included in the multivariable segmented Poisson regression model examining the effect of a change in hydromorphone presentation dose on hydromorphone administration. The variable "Prechange (2 mg→1 mg)" represents time (per 10 weeks) before the change in hydromorphone from a 2-mg to 1 mg unit dose. The variable "Change (2 mg→1 mg)" represents the change in presentation dose from 2-mg to 1-mg unit dose. The variable "Postchange" represents time (per 10 weeks) after the change in hydromorphone from a 2-mg to 1-mg unit dose. The variable "Change (1 mg→2 mg)" represents the change in unit dose presentation from 1 mg to 2 mg. The variable "Postchange (2 mg→1 mg)" represents time (per 10 weeks) after the change from a 1-mg to 2-mg unit dose. The variable "Anesthesia type" indicates the type of anesthesia administered to the patient (*i.e.*, general anesthesia [0], neuraxial anesthesia [1], and monitored anesthesia care [2]). The variable "Subspecialty" indicates the surgical subspecialty group to which the patient belonged (see the Materials and Methods section for description). ASA, American Society of Anesthesiologists Physical Status; ASA(E), ASA Physical Status emergency indicator.

Table 3.

Regression Coefficients with the Corresponding *P* Values and 95% CI for Predictors from the Hydromorphone Interrupted Time Series Analysis with a Continuous Outcome

Predictor	Effect (95% CI)	*P* Value
Change (2 mg→1 mg)	−0.11 (−0.16 to 0.06)	< 0.0001
Change (1 mg→2 mg)	0.09 (0.02 to 0.15)	0.008
Prechange (2 mg→1 mg)	0.00 (−0.01 to 0.00)	0.071
Postchange (2 mg→1 mg)	0.01 (−0.02 to 0.05)	0.478
Postchange (1 mg→2 mg)	−0.01 (−0.09 to 0.06)	0.764
Weight, 10-kg	0.03 (0.02 to 0.04)	< 0.0001
Body mass index, kg/m^2	0.00 (−0.01 to 0.00)	0.086
Age, 10-yr	−0.05 (−0.05 to −0.04)	< 0.0001
Sex, % male	−0.02 (−0.04 to 0.00)	0.101
ASA classification	0.01 (−0.01 to 0.02)	0.429
ASA(E)	−0.07 (−0.11 to −0.02)	0.009
Case duration, 60-min	0.06 (0.05 to 0.06)	< 0.0001
Ketamine	0.32 (0.28 to 0.36)	< 0.0001
Acetaminophen	−0.07 (−0.09 to −0.05)	< 0.0001
Ketorolac	0.03 (−0.01 to 0.06)	0.123
Subspecialty		< 0.0001
(0 *vs.* 2)	−0.23 (−0.31 to −0.15)	< 0.0001
(1 *vs.* 2)	−0.23 (−0.40 to −0.06)	0.007
Anesthesia type		0.0001
(0 *vs.* 2)	−0.14 (−0.21 to −0.07)	< 0.0001
(1 *vs.* 2)	−0.32 (−0.45 to −0.20)	< 0.0001

This table displays the coefficients, 95% CI, and *P* values for each of the variables included in the multivariable segmented linear regression model examining the effect of a change in hydromorphone presentation dose on hydromorphone administration. The variable "Prechange (2 mg→1 mg)" represents time (per 10 weeks) before the change in hydromorphone from a 2-mg to 1-mg unit dose. The variable "Change (2 mg→1 mg)" represents the change in presentation dose from 2-mg to 1-mg unit dose. The variable "Postchange" represents time (per 10 weeks) after the change in hydromorphone from a 2-mg to 1-mg unit dose. The variable "Change (1 mg→2 mg)" represents the change in unit dose presentation from 1 mg to 2 mg. The variable "Postchange (2 mg→1 mg)" represents time (per 10 weeks) after the change from a 1-mg to 2-mg unit dose. The variable "Anesthesia type" indicates the type of anesthesia administered to the patient (*i.e.*, general anesthesia [0], neuraxial anesthesia [1], and monitored anesthesia care [2]). The variable "Subspecialty" indicates the surgical subspecialty group to which the patient belonged (see the Materials and Methods section for description). ASA, American Society of Anesthesiologists Physical Status; ASA(E), ASA Physical Status emergency indicator.

Table 4.

Regression Coefficients with the Corresponding *P* Values and 95% CI for Predictors from the PACU Opioid Administration Interrupted Time Series Analysis

Predictor	Effect (95% CI)	*P* Value
Change (2 mg→1 mg)	1.55 (–0.33 to 3.43)	0.106
Change (1 mg→2 mg)	0.35 (–2.15 to 2.84)	0.784
Prechange (2 mg→1 mg)	0.00 (–0.20 to 0.20)	0.983
Postchange (2 mg→1 mg)	–1.36 (–2.82 to 0.10)	0.068
Postchange (1 mg→2 mg)	2.81 (–0.14 to 5.76)	0.062
Weight, 10-kg	0.99 (0.54 to 1.44)	< 0.0001
Body mass index, kg/m^2	–0.15 (–0.29 to –0.01)	0.031
Age, 10-yr	–1.36 (–1.59 to –1.13)	< 0.0001
Sex, % male	–1.37 (–2.30 to –0.44)	0.004
ASA classification	–0.14 (–0.72 to 0.44)	0.647
ASA(E)	–3.25 (–5.17 to –1.33)	0.001
Case duration, 60-min	–0.01 (–0.02 to –0.01)	< 0.0001
Ketamine	–14.15 (12.49 to 15.81)	< 0.0001
Acetaminophen	–0.96 (–1.74 to –0.19)	0.015
Ketorolac	0.77 (–0.64 to 2.18)	0.286
Subspecialty		< 0.0001
(0 *vs.* 2)	9.89 (6.88 to 12.91)	< 0.0001
(1 *vs.* 2)	9.99 (3.44 to 16.53)	0.003
Anesthesia type		< 0.0001
(0 *vs.* 2)	4.36 (1.60 to 7.13)	0.002
(1 *vs.* 2)	–1.48 (–6.39 to 3.43)	0.556

This table displays the coefficients, 95% CI, and *P* values for each of the variables included in the multivariable segmented linear regression model examining the effect of hydromorphone presentation dose on postanesthesia care unit (PACU) opioid administration. The variable "Prechange (2 mg→1 mg)" represents time (per 10 weeks) before the change in hydromorphone from a 2-mg to 1-mg unit dose. The variable "Change (2 mg→1 mg)" represents the change in presentation dose from 2-mg to 1-mg unit dose. The variable "Postchange" represents time (per 10 weeks) after the change in hydromorphone from a 2-mg to 1-mg unit dose. The variable "Change (1 mg→2 mg)" represents the change in unit dose presentation from 1 mg to 2 mg. The variable "Postchange (2 mg→1 mg)" represents time (per 10 weeks) after the change from a 1-mg to 2-mg unit dose. The variable "Anesthesia type" indicates the type of anesthesia administered to the patient (*i.e.*, general anesthesia [0], neuraxial anesthesia [1], and monitored anesthesia care [2]). The variable "Subspecialty" indicates the surgical subspecialty group to which the patient belonged (see the Materials and Methods section for description). ASA, American Society of Anesthesiologists Physical Status; ASA(E), ASA Physical Status emergency indicator.

Table 5.

Summary Statistics for Outcome Measures across the Three Cohorts with the *P* Values for the Change Points in the Corresponding Regression Models

	Cohort 1	Cohort 2	Cohort 3	*P* Value Change (2 mg→1 mg)	*P* Value Change (1 mg→2 mg)
Hydromorphone (binary)	2,183 (21.2%)	296 (10.3%)	226 (16.6%)	< 0.0001	0.008
Hydromorphone, mg	0.8 (0.6)	0.7 (0.5)	0.8 (0.7)	< 0.0001	0.008
PACU morphine milligram equivalents	15.6 ± 21.5	15.6 ± 21.9	15.6 ± 25.7	0.106	0.784
Intraoperative morphine milligram equivalents	38.7 ± 25.8	35.7 ± 24.8	34.22 ± 24.8	0.984	0.238
Intraoperative fentanyl, mcg	145.9 ± 111.4	139.0 ± 115.2	126.6 ± 104.5	0.245	0.111
Total encounter morphine milligram equivalents	54.2 ± 36.1	51.3 ± 36.6	49.8 ± 38.2	0.320	0.513
Admission PACU pain score	3.1 ± 3.7	3.5 ± 3.8	3.4 ± 3.7	0.316	0.068
Discharge PACU pain score	2.6 ± 2.6	2.8 ± 2.7	2.6 ± 2.7	0.536	0.214

Summary statistics for the outcome measures are reported for each of the three cohorts. Cohorts 1 and 3 refer to the time periods with a 2-mg unit dose presentation, and cohort 2 refers to the time period with a 1-mg unit dose presentation. Continuous variables are presented as mean ± SD, and categorical variables are presented as number (percentage). Hydromorphone (binary) represents the proportion of patients who were administered greater than 1 mg of hydromorphone intraoperatively. For each outcome variable, the *P* values for the change-points in the segmented regression models are provided. PACU, postanesthesia care unit.