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ORIGINAL RESEARCH

Optimizing intraoperative administration of propofol, remifentanil, and fentanyl through pharmacokinetic and pharmacodynamic simulations to increase the postoperative duration of analgesia

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Abstract

Titrating an intraoperative anesthetic to achieve the postoperative goals of rapid emergence and prolonged analgesia can be difficult because of inter-patient variability and the need to provide intraoperative sedation and analgesia. Modeling pharmacokinetics and pharmacodynamics of anesthetic administrations estimates drug concentrations and predicted responses to stimuli during anesthesia. With utility of these PK/PD models we created an algorithm to optimize the intraoperative dosing regimen. We hypothesized the optimization algorithm would find a dosing regimen that would increase the post-operative duration of analgesia, not increase the time to emergence, and meet the intraoperative requirements of sedation and analgesia. To evaluate these hypotheses we performed a simulation study on previously collected anesthesia data. We developed an algorithm to recommend different intraoperative dosing regimens for improved post-operative results. To test the post-operative results of the algorithm we tested it on previously collected anesthesia data. An anesthetic dataset of 21 patients was obtained from a previous study from an anesthetic database at the University of Utah. Using the anesthetic records from these surgeries we modeled 21 patients using the same patient demographics and anesthetic requirements as the dataset. The anesthetic was simulated for each of the 21 patients with three different dosing regimens. The three dosing regimens are: from the anesthesiologist as recorded in the dataset (control group), from the algorithm in the clinical scenario one (test group), and from the algorithm in the clinical scenario two (test group). We created two clinical scenarios for the optimization algorithm to perform; one with normal general anesthesia constraints and goals, and a second condition where a delayed time to emergence is allowed to further maximize the duration of analgesia. The algorithm was evaluated by comparing the post-operative results of the control group to each of the test groups. Comparing results between the clinical scenario 1 dosing to the actual dosing showed a median increase in the duration of analgesia by 6 min and the time to emergence by 0.3 min. This was achieved by decreasing the intraoperative remifentanil infusion rate, increased the fentanyl dosing regimen, and not changing the propofol infusion rate. Comparing results between the clinical scenario 2 dosing to the actual dosing showed a median increase in the duration of analgesia by 26 min and emergence by 1.5 min. To dosing regimen from clinical scenario 2 greatly increased the fentanyl dosing regimen and greatly decreased the remifentanil infusion rate with no change to the propofol infusion rate. The results from this preliminary analysis of the optimization algorithm appear to imply that it can operate as intended. However a clinical study is warranted to determine to what extent the optimization algorithm determined optimal dosing regimens can maximize the postoperative duration of analgesia without delaying the time to emergence in a clinical setting.

Keywords Anesthesia · Pharmacokinetic · Pharmacodynamic · Total intravenous anesthesia · Optimization

1 Introduction

Anesthesiologists titrate their anesthetic to not only provide adequate intraoperative analgesia and maintain unresponsiveness, but also to provide a timely emergence and lengthy postoperative analgesia. Titrating an anesthetic to achieve these goals can be difficult because of inter-patient

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variability and differences in postoperative pain. The difficulty in providing an extended postoperative analgesia is further compounded due to the possible negative effects of postoperative hyperalgesia and intolerable ventilatory depression.

Researchers have developed pharmacokinetic (PK) and interaction pharmacodynamic (PD) models that describe concentration changes over time and interactions between sedatives and opioids interact for selected drug effects (e.g., loss of responsiveness, loss of response to painful stimuli, etc.) [1–11]. These models have been used to identify dosing regimens of selected anesthetics to optimize time to emergence [12] and drive displays that present predicted drug concentrations and effects real time [13]. Preliminary clinical use of the PK/PD models embedded in drug displays suggests they may improve anesthetic dosing consistency [14]. Further work has developed PK/PD based closed-loop controllers to optimize titrate remifentanil and propofol to better maintain intraoperative BIS values and shorten emergence time [15]. Theoretical application of these PK/PD models propose development of algorithms to optimize both the hypnotic and analgesic anesthetic drug administration [16, 17]. Thus PK/PD models may be useful in exploring anesthetic dosing to not only minimize time to emergence but also prolong postoperative analgesia.

We built an optimization algorithm based on published PK and PD models to explore possible intraoperative analgesic and sedative dosing regimens that would have minimal impact on the time to emergence but prolong analgesia after emergence. The optimization algorithm was constrained to maintain intraoperative sedation and analgesia as well as to avoid postoperative hyperalgesia and intolerable ventilatory depression.

To evaluate our algorithm, we conducted a preliminary analysis comparing the predicted time to emergence and duration of analgesia in simulations of actual anesthetic dosing regimens with simulations of algorithm derived anesthetic dosing regimens. We hypothesized that the algorithm is able to propose adjustments in intraoperative dosing to obtain predefined postoperative outcome measures. We tested two different simulations and compare the resulting postoperative outcomes with the original outcomes when titration is performed according to the anesthesiologist's discretion.

2 Methods

2.1 Overview

We developed an algorithm to recommend intraoperative dosing regimens for improved post-operative results. To test the post-operative results of the algorithm we tested it on previously collected anesthesia data. We modeled 21 patients using the same patient demographics and anesthetic requirements as the dataset. The anesthetic was simulated for each of the 21 patients with three different dosing regimens; one control group and two test groups. The algorithm was evaluated by comparing the post-operative results of the control group to each of the two test groups.

2.2 Patient data collection

Data for this simulation study was obtained from a previously published study [10]. In brief, after internal review board and obtaining written informed consent, in a prospective study, a convenience sample of perioperative data from 21 patients undergoing a general anesthetic with endotracheal intubation for elective surgery at the University of Utah Health from November 2005 to January 2006 were collected. In this prior study, the anesthetic technique was confined to a total intravenous anesthetic using propofol, fentanyl, and remifentanil for induction and maintenance of anesthesia and fentanyl for post-operative pain control in the post anesthesia care unit (PACU). Intraoperative dosing regimens were titrated per the anesthesiologists' discretion. The perioperative data included patient demographics, details of the anesthetic, type of surgical procedure, and post-surgery period, and timing of key events throughout the perioperative period. The patient demographics recorded were the age, height, weight, sex, American Society of Anesthesiologist Physical Status classification. The key events included the timing and dose of propofol, fentanyl, and remifentanil for induction and anesthetic maintenance, the time of termination of the anesthetic, time of emergence, and the time of the first fentanyl administration in the PACU.

Three time periods were calculated, anesthetic duration, time to emergence, and time to first fentanyl administration in the PACU. The anesthetic duration was defined as the time from the initial dose to the termination of all anesthetics. The time to emergence was defined as the time from termination of all anesthetics to time of first responding to a prompt to follow a command. A study investigator prompted the patient every 20 s for a response. The time to first post-operative fentanyl administration was defined the time from termination of anesthetic to time to first fentanyl administration in the PACU. For discussion purposes, this time period was established as the "duration of post-operative analgesia".

2.3 Optimization algorithm development

Published PK and PD models were used to build an anesthetic dosing optimization algorithm (here to for referred to as the "algorithm") that recommended propofol, remifentanil, and fentanyl dosing regimens for maintenance of

anesthesia. A brief overview of the algorithm will be described here, but details of the algorithm's methods are presented in Online Supplement 1.

Three response surface interaction models were used in the algorithm: one that predicts unresponsiveness [8], another that predicts the probability of analgesia [9], and a third that predicts the probability of intolerable ventilatory depression [11]. Dosing recommendations were made every 20 min. Inputs into the algorithm included patient demographic information, induction and maintenance doses of propofol, fentanyl, and remifentanil real time (e.g., the available dosing history), and an estimate of the time to termination of the anesthetic. Outputs from the algorithm included recommendations for continuous infusion rates of propofol and remifentanil with intermittent bolusing for fentanyl every 20 min.

Using this algorithm, we explored (through simulations) possible fentanyl, propofol, and remifentanil dosing regimens for two clinical scenarios. In the first scenario, the algorithm was constrained to obtain recommended doses that would prolong post-operative analgesia without prolonging the time to emergence. This scenario was designed to mimic an anesthetic that allows for a timely emergence but also provides as much post-operative analgesia as possible for procedures associated with moderate post-operative pain. In the second scenario, the algorithm was constrained to obtain recommended doses that would prolong post-operative analgesia allowing a slight delay (up to 3 min) in the time to emergence. This scenario was designed to mimic an anesthetic that provides a longer period of post-operative analgesia for procedures associated with severe post-operative pain at the expense of a small delay in the time to emergence.

2.4 Defining postoperative emergence and analgesia

To determine when the algorithm would assume a patient would emerge and have insufficient analgesia we developed non-response to response thresholds. The thresholds chosen were isoboles from the response surface interaction models. The thresholds were chosen using the previously collected dataset.

To explore the choice of thresholds for each effect plots were prepared. Using dosing regimens from the previously collected dataset (Online Supplement 2), predicted remifentanil equivalent–propofol effect site concentration pairs were plotted at the time of emergence and at the time of the first dose of fentanyl in the PACU. Selected remifentanil–propofol predicted iso effect lines, or "isoboles" from the pharmacodynamic interaction models responsiveness [8], analgesia [9], and ventilatory depression [11] were layered over the predicted remifentanil equivalent–propofol concentration pairs. The thresholds chosen was the isobole that best fit the plotted remifentanil equivalent-propofol concentrations pairs. The best fit was the isobole where approximately half of the concentration pairs were above and the remaining were below that isobole. Specifically, the pharmacodynamic probability of responsiveness and intolerable ventilatory depression isoboles were layered over the predicted concentration pairs at the time of emergence to establish the threshold for responsiveness and intolerable ventilator depression. And the pharmacodynamic probability of analgesia isoboles were layered over the predicted concentration pairs at the time of the first fentanyl dose in the PACU to establish the threshold for analgesia.

The predicted time to emergence was defined as the time from terminating all anesthetics to the time at which the pharmacodynamic probability of responsiveness was less than the responsiveness threshold, as described above. The pharmacodynamic probability of unresponsiveness was defined as no response to a verbal and painful tactile prompt [8]. The predicted duration of post-operative analgesia was defined as the time from terminating all anesthetics to the time at which the pharmacodynamic probability of analgesia was less than the analgesia threshold. The pharmacodynamic probability of analgesia was defined as no response to 50 pounds per square inch of pressure on the anterior tibia [9]. The predicted duration of intolerable ventilatory depression was defined as the time from terminating all anesthetics to the time at which the pharmacodynamic probability of intolerable ventilatory depression was less than the intolerable ventilator depression threshold. The pharmacodynamic probability of intolerable ventilatory depression was defined as less than four breaths per minute in an unstimulated state [11].

2.5 Application of the optimization algorithm

A set of simulations were performed to predict the time to emergence, duration of post-operative analgesia, and duration of postoperative ventilatory depression. Three simulations were performed for each of the 21 patients included in this analysis. The first simulation used the actual propofol, fentanyl, and remifentanil dosing as delivered by the anesthesiologist caring for the patient (called "actual dosing"). The second simulation used the dosing regimens as recommended from the algorithm during clinical scenario 1 (called "clinical scenario 1 dosing"). And the third simulation used the dosing regimens as recommended from the algorithm during clinical scenario 2 (called "clinical scenario 2 dosing"). For simulation purposes, predicted fentanyl effect site concentrations were converted to remifentanil effect site concentrations using the 1:1.2 [1] and added to the predicted remifentanil effect site concentrations. Total opioid

concentrations were labeled predicted remifentanil equivalent effect site concentrations.

Predicted times to emergence and duration of post-operative analgesia were the primary outcome measures used to make comparisons between the three scenarios described above for each patient. The time to emergence and duration of analgesia for the control group were not the observed times, but rather the predicted times as predicted for the simulated clinical scenarios. For discussion purposes, a difference of increasing the duration of analgesia of 6 min or more while minimizing the time to emergence within 3 min of when the patients actually emerged from anesthesia were considered clinically useful. The secondary outcome measures were the duration of ventilatory depression and the combined maximum of the time to emergence and the duration of ventilatory depression. Since emergence and ventilatory drive precede extubation the combined emergence and ventilatory depression time was a metric for us to compare the duration of possible extubation readiness of the patient with the different dosing regimens. As this was a preliminary analysis with a convenience sample of 21 patients, no a priori power analysis was conducted. As such, the findings from this study are to be considered preliminary and hypothesis generating.

2.6 Statistical analysis

Statistical analysis was performed using SigmaPlot Version 13.0 (Systat Software, San Jose, CA). The predicted duration of analgesia and the time to emergence were presented as individual times for each subject. This data was found to have a non-normal distribution and therefore summarized with medians and interquartile ranges. The primary outcomes measures, the time to emergence and the duration of analgesia, were compared with a repeated measures ANOVA on ranks (a non-parametric equivalence to ANOVA). A Turkey's test was used for posthoc pairwise multiple comparisons among the three dosing regimens; $p < 0.05$ was considered statistically significant. The secondary outcome measures, the duration of ventilatory depression and the combined time to emergence and duration of ventilatory depression, were compared with a repeated measures ANOVA on ranks.

3 Results

3.1 Patient data collection

Previously published patient data were used in this simulation study [10]. Patient demographics and surgical procedures are presented in supplement Tables 1 and 2. Propofol, fentanyl, and remifentanil dosing regimens are presented in Online Supplement 2. The observed duration of the anesthetic, time to emergence, and timing of first fentanyl administration in the post anesthesia care unit are presented in Table 1.

Through analysis of the results from the previously collected data we defined how the algorithm would estimate a patient's threshold from non-responsive to responsive. The algorithm assumes each individual threshold is an isobole on the response surface interaction model. The threshold isoboles were determined as follows. A set of plots of predicted remifentanil equivalent–propofol concentration pairs at the observed time of emergence and at the observed time of the first fentanyl dose in the PACU are presented in Fig. 1. Layered over this data are the 1, 5, 50, and 95% isobole lines for response surface interaction models of unresponsiveness and probability of intolerable ventilatory depression at the time of emergence and probability of analgesia at the time of first fentanyl dose in the PACU. Panel A shows the pharmacodynamic isoboles for the probability of unresponsiveness and the predicted remifentanil equivalent–propofol concentration pairs at the observed time of emergence. The 50% isobole (indicated by the arrow) best dissects the concentration pairs. The 50% isobole was set as the threshold where the algorithm predicted each patient would emerge during simulations. Panel B shows the pharmacodynamic isoboles for the probability of analgesia and the predicted remifentanil equivalent–propofol concentration pairs at the observed time of first fentanyl dose in the PACU. The 1% isobole (indicated by the arrow) best dissects the concentration pairs. The 1% isobole was set as the threshold where the algorithm predicted each patient would require additional analgesia. Panel C shows the pharmacodynamic isoboles for the probability of intolerable ventilatory depression and the predicted remifentanil equivalent–propofol concentration pairs at the observed time of emergence. The 50% isobole (indicated by the arrow) best dissects the concentration pairs. The 50% isobole was set as the threshold where the algorithm predicted each patient would no longer have intolerable ventilatory depression.

3.2 Optimization algorithm simulation testing

An example of predicted concentrations and effects from the actual dosing, clinical scenario 1 dosing, and clinical scenario 2 dosing for one of the patients is presented in Figs. 1 and 2. The clinical scenario 1 and 2 dosing regimens were determined by implementing the algorithm for clinical scenario 1 (prolong analgesia while minimally changing the time to emergence) and clinical scenario 2 (prolong analgesia allowing a slight delay to the time to emergence). The plots present the resultant predicted effect site concentrations for each drug (fentanyl, propofol, and remifentanil) and associated predicted drug effects (time to emergence,

Table 1 Observed anesthetic duration, time to emergence, and time to first opioid administration in the post anesthesia care unit

Subject	Anesthetic duration (min)	Time to emergence (min)	Time to first fentanyl dose in PACU (min)
1	218	1.4	23.2
2	67	3.0	17.9
3	372	10.4	46.1
4	25	0.5	10.2
5	175	6.1	20.3
6	228	13.0	39.3
7	61	14.8	22.2
8	42	3.0	6.8
9	46	18.3	29.5
10	92	1.7	14.7
11	195	4.3	19.8
12	91	3.3	20.7
13	202	1.8	21.0
14	38	15.5	29.9
15	63	2.9	14.6
16	52	7.7	12.6
17	137	2.6	18.2
18	190	7.8	30.4
19	112	1.0	19.3
20	52	7.7	12.7
21	275	15.8	30.2
Median [IQR]	92 [52–195]	4.3 [1.8–10.4]	20.3 [14.6–29.5]

PACU post anesthesia care unit

Table 2 Actual and algorithm derived remifentanil, propofol, and fentanyl dosing regimens

	Actual dosing	Clinical scenario 1 dosing	Clinical scenario 2 dosing
Remifentanil infusion (mcg/kg/min)	0.21 [0.13–0.25]	0.11 [0.06–0.15]	0.01 [0–0.06]
Propofol infusion (mcg/kg/min)	120 [112–133]	108 [89–123]	110 [97–134]
Fentanyl bolusing (mcg/kg/20 min)	0.3 [0.1–0.6]	1.4 [0.8–2.6]	2.8 [2.0–3.0]

Data presented as median [inter quartiles]

The actual fentanyl dosing regimen is converted from isolated boluses to weight adjusted 20 min interval boluses

duration of analgesia, duration of ventilatory depression) for one of the patients in this study. In this example, the predicted time to emergence increased from 4.3 min (actual dosing) to 5.7 or 7.2 min (clinical scenario 1 dosing and clinical scenario 2 dosing); however, the duration of analgesia also increased from 13.2 min (actual dosing) to 27.2 and 32.8 min (clinical scenario 1 dosing and clinical scenario 2 dosing). A similar set of plots for all patients is presented in Online Supplement 3.

The actual and algorithm recommended doses are presented in Table 2. For clinical scenario 1, the algorithm recommended an increase in fentanyl [$\Delta + 1.1$ mcg/kg/20 min], a decrease in remifentanil [$\Delta - 0.10$ mcg/kg/min], and little change to the propofol dosing [$\Delta - 12$ mcg/kg/min]. The recommended increase in fentanyl was a function of the duration of the anesthetic (Fig. 3). As the duration of the surgical procedure increased, the total amount of fentanyl increased. By contrast, the actual fentanyl dosing consisted of 100–250 mcg boluses near the end of surgery, regardless of the duration of surgery.

For clinical scenario 2, the algorithm recommended a large increase in fentanyl [$\Delta + 2.5$ mcg/kg/20 min], a large decrease in remifentanil [$\Delta - 0.20$ mcg/kg/min], and little change to the propofol dosing [-10 mcg/kg/min]. As with clinical scenario 1, the recommended increase in fentanyl

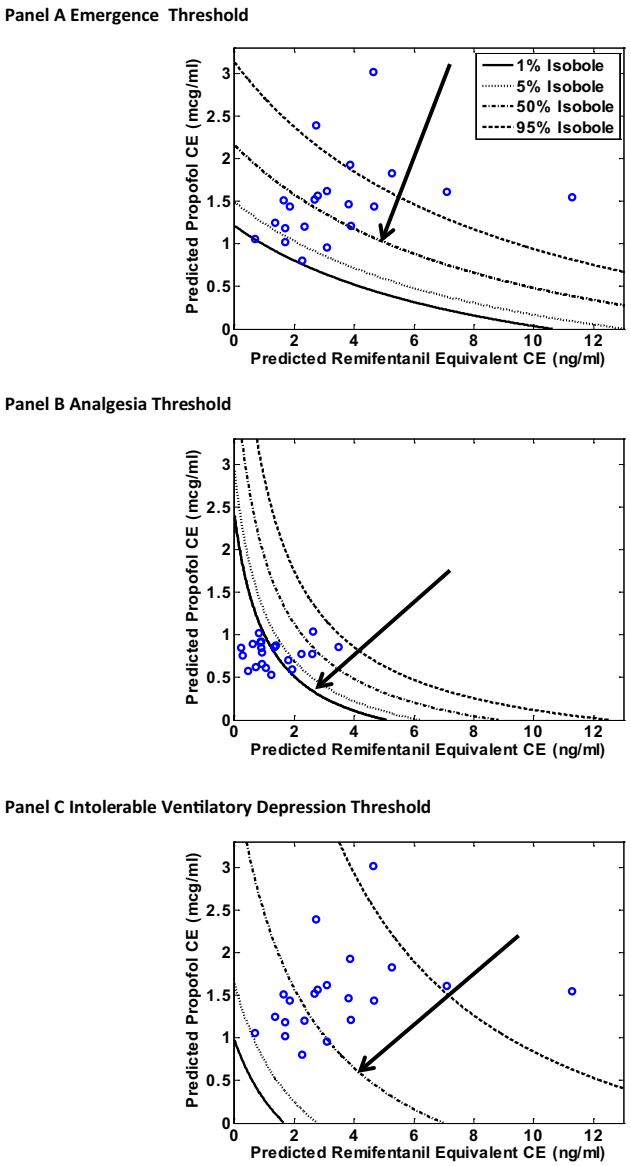


Fig. 1 Shown are the predicted propofol–remifentanil equivalent effect site concentrations (CE) following the dosing regimens described in Online Supplement 2 and pharmacodynamic isoboles for unresponsiveness, analgesia, and intolerable ventilatory depression. The isoboles indicates the propofol–remifentanil effect site concentration pairs that are predicted to produce the same effect, i.e., the 95% isobole indicates the propofol-remifentanil effect site concentrations that elicit no response in 95% of patients. The 1% (solid), 5% (dotted), 50% (dash-dot), and 95% (dashed) isoboles are shown in black lines in each panel. Panel **a** the predicted propofol–remifentanil equivalent effect site concentrations at emergence and the isobole curves predicting the probability of no responsiveness. The 50% isobole, as indicated by the arrow, is the algorithm's indicated threshold for emergence. Panel **b** the predicted propofol–remifentanil equivalent effect site concentrations at the time of first fentanyl dose in the PACU and the isobole curves predicting the probability of no response to a moderately painful stimulus. The 1% isobole, as indicated by the arrow, is the algorithm's indicated threshold for analgesia. Panel **c** the predicted propofol–remifentanil equivalent effect site concentrations at emergence and the isobole curves predicting the probability of intolerable ventilatory depression. The 50% isobole, as indicated by the arrow, is the algorithm's indicated threshold for intolerable ventilatory depression

was a function of the duration of the anesthetic (Fig. 3). As duration increased, the total amount of fentanyl increased.

3.3 Primary and secondary outcome measure results

The predicted time to emergence, duration of post-operative analgesia, and duration of intolerable ventilatory depression are presented in Fig. 4 and Table 3. For clinical scenario 1 by comparison to the actual dosing, the algorithm prolonged the duration of post-operative analgesia by a median of 6 min with an increase in the time to emergence by a median of 0.3 min; it also decreased the duration of intolerable ventilatory depression. For clinical scenario 2 by comparison to the actual dosing regimen, the algorithm prolonged the duration of post-operative analgesia by a median of 26 min with an increase in the time to emergence by a median of 1.5 min; as well as increased the duration of intolerable ventilatory depression and the combined time to emergence and duration of intolerable ventilatory depression (Fig. 5). Overall, there were statistical significant differences in the time to emergence ($\chi^2 = 40.1$, df = 2, $p < 0.001$) and the duration of analgesia ($\chi^2 = 35.3$, df = 2, $p < 0.001$) due to dosing regimen. Pairwise comparisons (Tukey's test results) are shown in Fig. 6.

4 Discussion

In this preliminary analysis, our results suggest that an optimization algorithm can identify dosing regimens of propofol, remifentanil, and fentanyl that increase the postoperative duration of analgesia. We explored the utility of this algorithm with two clinical scenarios. In clinical scenario 1, the aim was to prolong analgesia with minimal change in the time to emergence. With this constraint, the algorithm recommended an increase in intraoperative fentanyl administration and a decrease in remifentanil administration. This intraoperative dosing change led to a modest increase in the duration of post-operative analgesia with a small decrease in the combined time to emergence and respiratory depression (Table 3). These findings met our criteria for potentially clinically useful with an increase in the duration of post-operative analgesia of 6 min or more while minimizing an increase in the time to emergence to less than 3 min. This may be somewhat useful in the PACU, especially when first arriving in the PACU. In this time period, there are several tasks to include attaching the patient to monitors and hand off reports from the operating room nurse and anesthesiologist to the PACU nurse that may benefit from not having to address pain control at the same time. We interpret the results to imply that the full pharmacologic benefit of fentanyl (as compared to remifentanil) is not fully realized

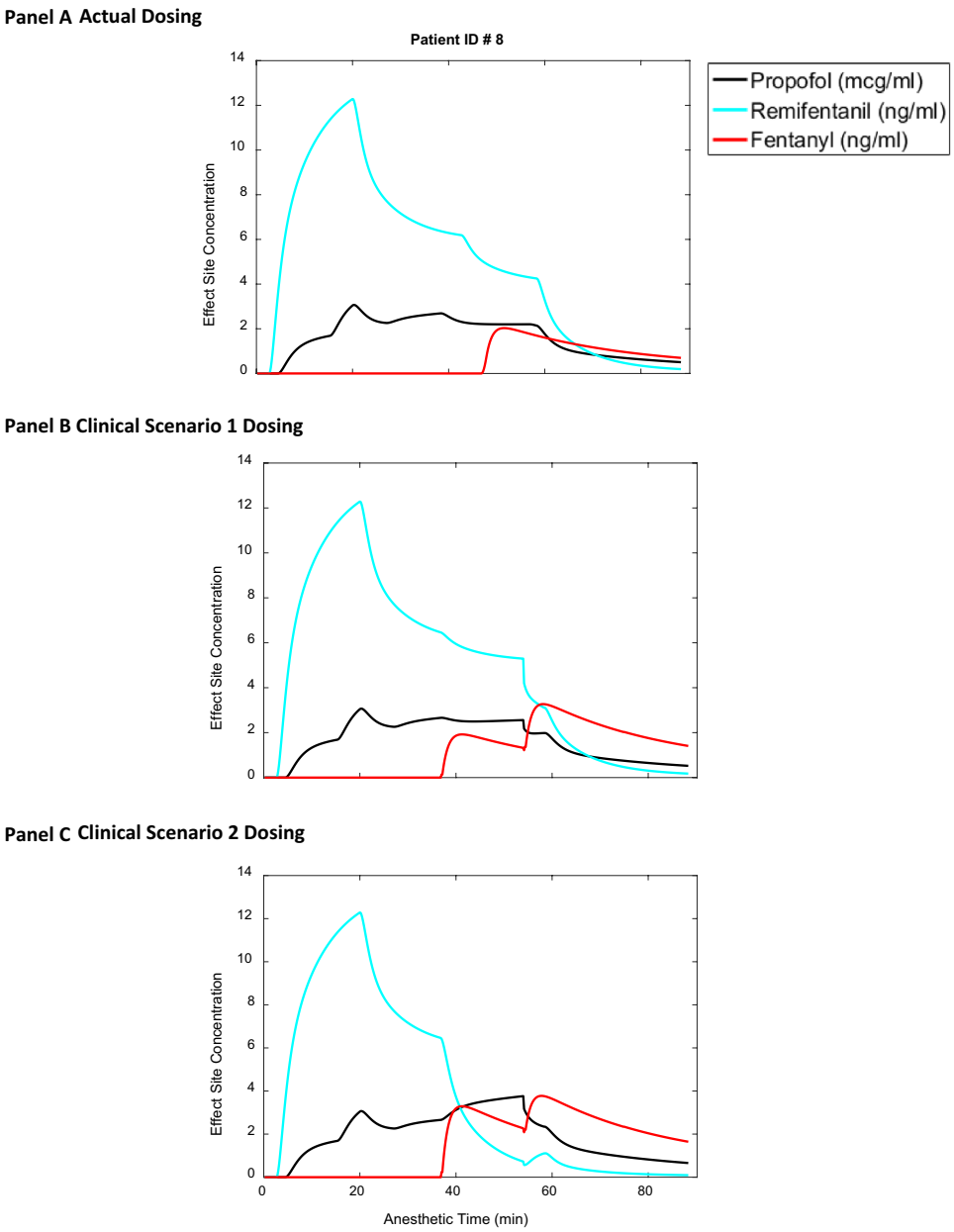


Fig. 2 An example of predicted effect site concentrations from the actual dosing (Panel **a**), clinical scenario 1 dosing (Panel **b**), and clinical scenario 2 dosing (Panel **c**)

when only administered as a transition opioid near the end of surgery. Specifically, fentanyl pharmacokinetics are slower than those of remifentanil; thus if fentanyl can be maintained at a basal level intraoperatively—low enough to not prolong emergence—it can significantly prolong the postoperative analgesia effect.

With regard to algorithm derived dosing for clinical scenario 1, the main difference from actual dosing, as presented in Fig. 1 and Table 2, was how fentanyl was dosed. With this scenario, incremental fentanyl dosing started just after the start of the anesthetic (< 30 min) and continued until < 30 min prior to the termination of all anesthetics. This led to a larger cumulative dose compared to the actual dosing. For example, assuming a 75 kg individual and a 2 h procedure, the total fentanyl dose recommended by the algorithm during the anesthetic would be 8.4 mcg/kg (630 mcg). This is in contrast to the actual dosing where fentanyl was not administered until just before the end of the anesthetic. The actual dosing would be 3.6 mcg/kg (270 mcg) administered once 20–30 min before the end of the anesthetic. Of note, with a larger fentanyl dose, the remifentanil dose was also reduced. Even amidst the increased fentanyl dosing most of the patients were predicted to have a shorter period post-operative ventilatory depression for this scenario.

For clinical scenario 2, the aim was to recommend doses that led to an increase in the duration of post-operative

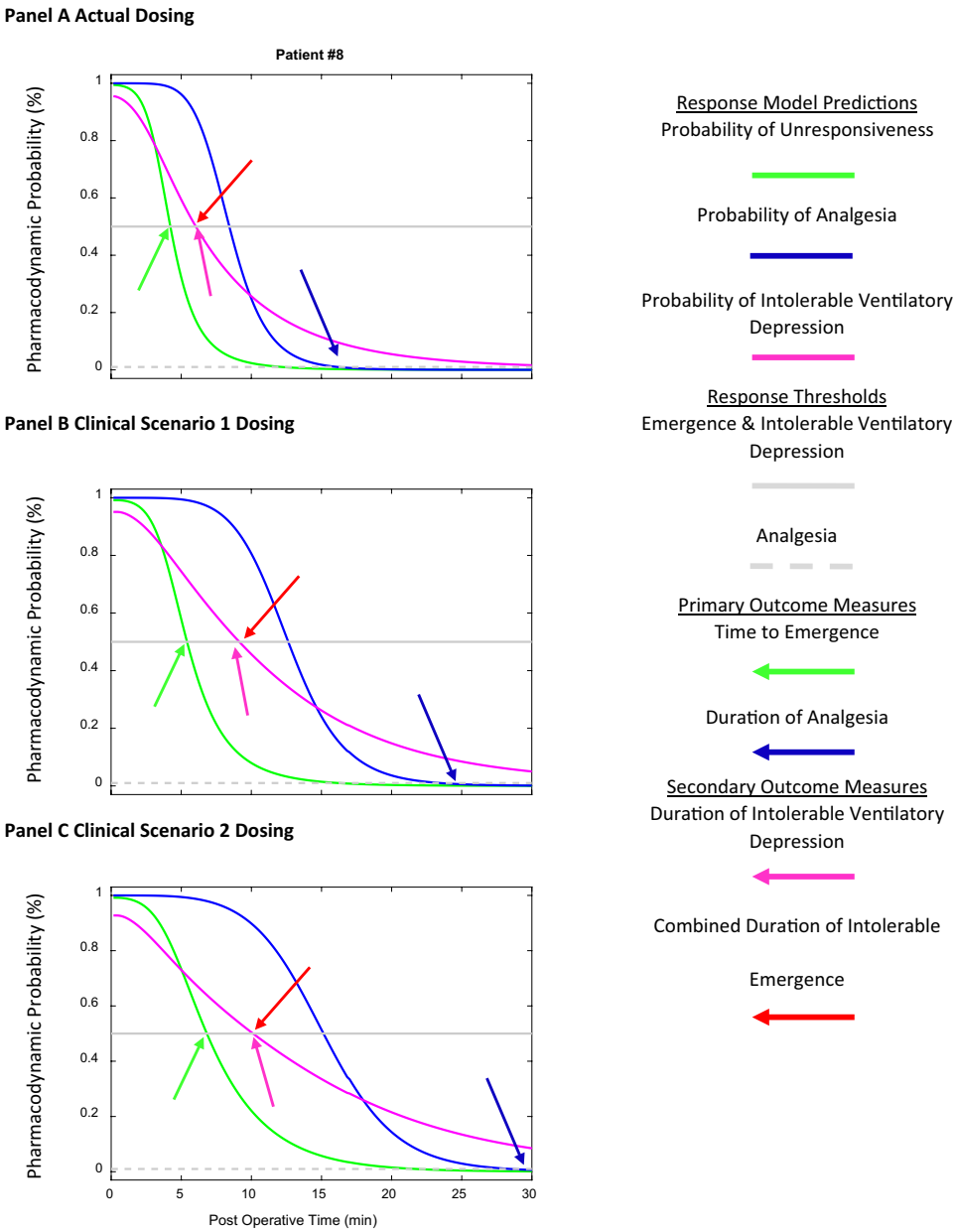


Fig. 3 An example of predicted drug effects, unresponsiveness, analgesia, and intolerable ventilatory depression from the actual dosing (Panel **a**), clinical scenario 1 dosing (Panel **b**), and clinical scenario 2 dosing (Panel **c**). The horizontal solid and dashed gray lines represent drug effect thresholds for time to emergence and duration of analgesia respectively. The time to emergence threshold (0.5) was defined as a 50% probability of being responsive to a verbal prompt with or without a tactile stimulus. The duration of analgesia threshold (0.01) was defined as a 1% probability of no response to a moderately painful stimulus

analgesia with a slight increase in the time to emergence. As expected, this approach prolonged post-operative analgesia but also increased the time to emergence and prolonged the duration of a high probability of ventilatory depression which may increase the time until extubation. This dosing approach may be useful in procedures associated with significant post-operative pain when there is no intent to extubate a patient immediately in the post-operative period.

To accommodate a much larger fentanyl dosing rate (e.g., median rate of 2.8 mcg/kg/20 min) than in clinical scenario 1, the algorithm targeted a low remifentanil high fentanyl concentration that allowed for persistent high fentanyl dosing throughout the procedure. This approach provided a prolonged dissipation of fentanyl once the anesthetic was terminated. This dosing regimen also calls for a substantial fentanyl dose.

In clinical scenario 2, as with clinical scenario 1, incremental fentanyl dosing started just after the start of the anesthetic and continued until near the end of the anesthetic. The major difference was the size of the incremental dose (median dose of 2.8 mcg/kg every 20 min). When compared to actual dosing, this led to a larger cumulative dose. Again, assuming a 75 kg individual and a 2-h procedure, the total fentanyl dose recommended by the algorithm

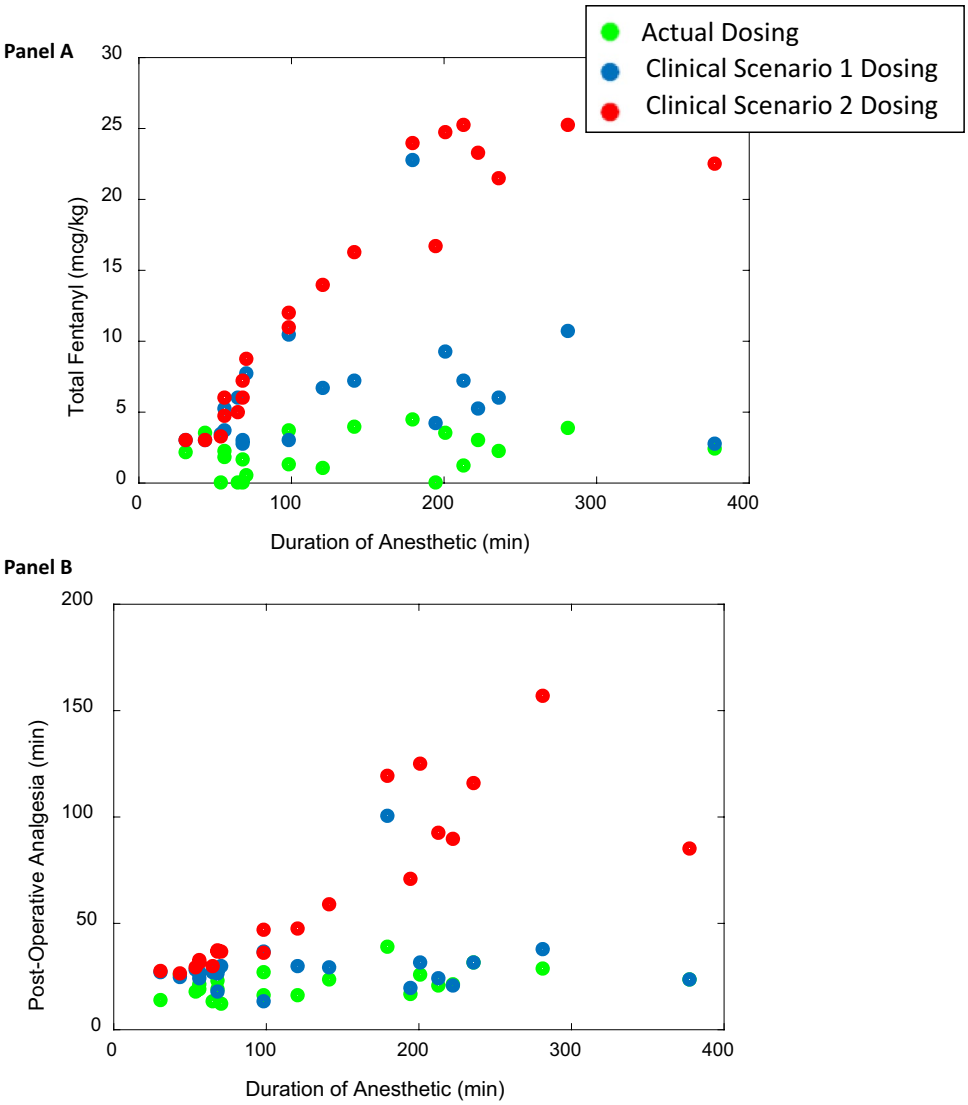
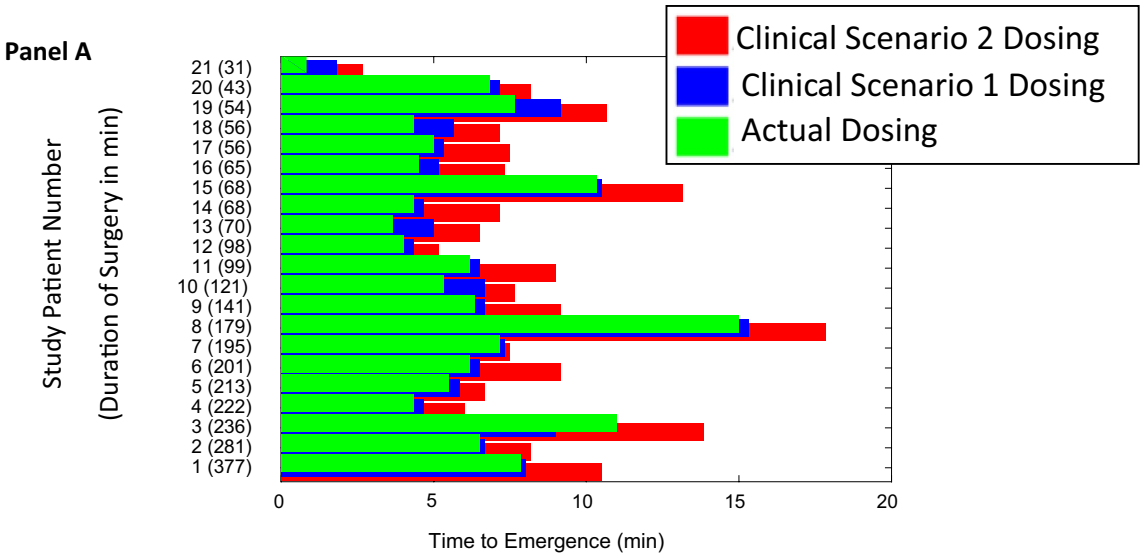
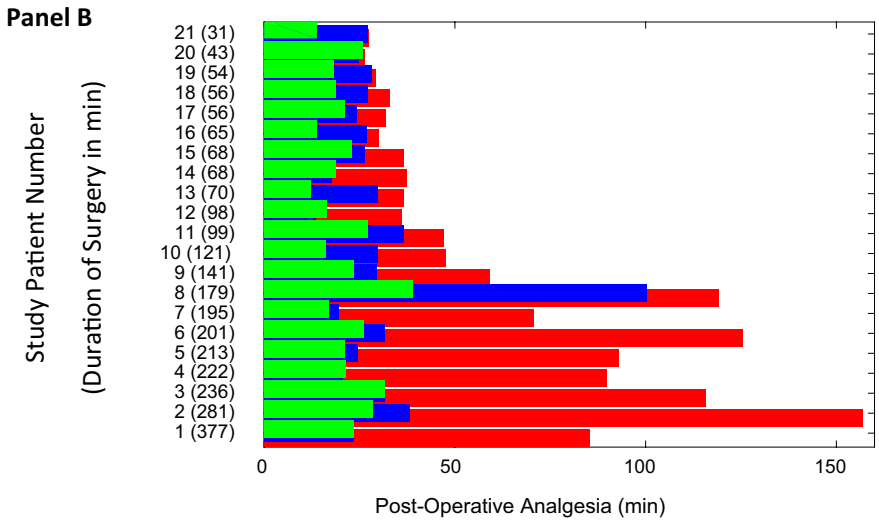


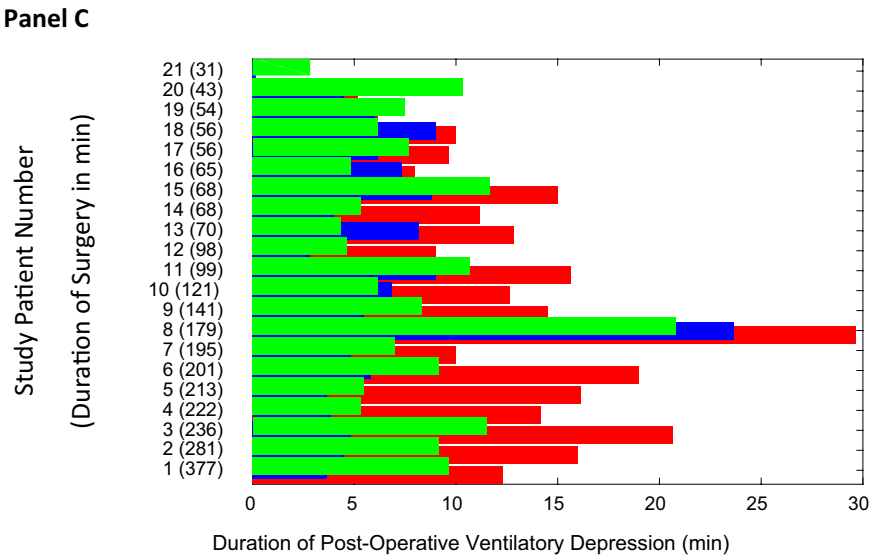
Fig. 4 Scatterplots illustrating the impact of the duration of the anesthetic on algorithm derived fentanyl dosing. Panel **a** presents the duration of the anesthetic versus the total weight normalized fentanyl dose. Panel **b** presents the duration of anesthetic versus the duration of post-operative analgesic effect. Actual dosing is represented by green dots, clinical scenario 1 dosing is represented by blue dots, and clinical scenario 2 dosing is represented by red dots for each of the 21 patients

during the anesthetic would be 16.8 mcg/kg (1260 mcg). This represents a fourfold increase in fentanyl administration. Accounting for the synergistic interaction between opioids and propofol and using interaction models to explore a range of opioid–propofol concentration pairs suggest that this approach is feasible.

This study is a preliminary proof of concept before real patients would be considered. The major limitation to this study is that it is a simulation analysis. There are several limitations to simulation analysis. First, the power of this analysis is unknown to properly explore the hypothesis. As such the results should be considered as suggestive and hypothesis generating only. Confirmatory work is required with a larger sample size to make definitive conclusions. Second, the algorithm did not account for how the recommended doses would impact patient hemodynamics or perform in the presence of intravascular volume depletion (e.g., from blood loss or dehydration). A clinical trial measuring the hemodynamic response under these conditions to algorithm dosing is warranted. Third, the impact of interpatient variability on predictions of combined drug effects may obscure potential improvements in the duration of post-operative analgesia [18]. As such, implementation of clinical scenario 1 in a clinical setting may lead to imperceptible changes in the duration of post-operative analgesia. Fourth, the algorithm dosing recommendations require frequent propofol and remifentanil infusion rate adjustments and bolus fentanyl dosing (e.g., dosing adjustments every 20 min). The algorithm in the simulation followed the dosing recommendations immediately. Clinicians will likely find this intolerable and not follow the dosing recommendations unless somehow automated. If the anesthesiologists delay or don't adjust the


Panel A
Clinical Scenario 2 Dosing
Clinical Scenario 1 Dosing
Actual Dosing
Study Patient Number
(Duration of Surgery in min)
21 (31)
20 (43)
19 (54)
18 (56)
17 (56)
16 (65)
15 (68)
14 (68)
13 (70)
12 (98)
11 (99)
10 (121)
9 (141)
8 (179)
7 (195)
6 (201)
5 (213)
4 (222)
3 (236)
2 (281)
1 (377)
0
5
10
15
20
Time to Emergence (min)


Panel B
Study Patient Number
(Duration of Surgery in min)
21 (31)
20 (43)
19 (54)
18 (56)
17 (56)
16 (65)
15 (68)
14 (68)
13 (70)
12 (98)
11 (99)
10 (121)
9 (141)
8 (179)
7 (195)
6 (201)
5 (213)
4 (222)
3 (236)
2 (281)
1 (377)
0
50
100
150
Post-Operative Analgesia (min)


Panel C
Study Patient Number
(Duration of Surgery in min)
21 (31)
20 (43)
19 (54)
18 (56)
17 (56)
16 (65)
15 (68)
14 (68)
13 (70)
12 (98)
11 (99)
10 (121)
9 (141)
8 (179)
7 (195)
6 (201)
5 (213)
4 (222)
3 (236)
2 (281)
1 (377)
0
5
10
15
20
25
30
Duration of Post-Operative Ventilatory Depression (min)

◂**Fig. 5** Predicted time to emergence (Panel A), duration of post-operative analgesia (Panel B), duration of intolerable ventilatory depression (Panel C) for the actual dosing (green line), clinical scenario 1 dosing (blue line), and clinical scenario 2 dosing (red line) for each of the 21 patients. The numbers to the left represent the patient number sorted by duration of anesthesia, from longest to shortest. Values in parentheses represent the duration of the anesthetic

dose per the advice of the optimization algorithm the outcomes may be inaccurate and less impactful than as predicted. Fifth, with recent trends in administering combined anesthetics that de-emphasize opioid use, the optimization presented here may be of minimal clinical impact. Sixth, we chose to optimize fentanyl delivery. As an opioid with an intermediate duration of effect, our results were likely limited to the pharmacokinetic profile of fentanyl. It is likely that if we had used hydromorphone, an opioid with a long duration of effect, we would have reported findings that substantially prolonged the duration of post-operative analgesia in both scenarios. We chose to confine our analysis to fentanyl based on the patient data available to us where only fentanyl was used in addition to propofol and remifentanil. Seventh, use of the optimization algorithm is theoretical and yet remains unvalidated. It is unclear if the theoretical results can yield improvements in a clinical setting. Furthermore, the theoretical results are based on non-response to response thresholds we defined and are not expected to be accurate for each patient [19].

In summary, an optimization algorithm based on published pharmacokinetic and opioid-sedative pharmacodynamic interaction models was built to recommend intraoperative dosing of propofol, fentanyl, and remifentanil. We hypothesized that dosing regimens exist that would increase the postoperative duration of analgesia and do not increase the time to emergence. When implementing the algorithm, we found that dosing regimens exist that provide a modest increase in the duration of post-operative analgesia with minimal impact on time to emergence and conditions of unresponsiveness combined with ventilatory depression. We also explored algorithm dosing recommendations when the emergence could be slightly delayed. We report dosing regimens exist that substantially prolong post-operative analgesia but do delay the time to emergence. The main change in dosing was an increase in intraoperative fentanyl administration and a decrease in remifentanil administration. The successful results from this study implies that there are untapped improvements that are possible when PK/PD principles are applied. In particular, (1) the post-operative emergence and analgesia effects can be altered by changing intraoperative anesthetic administrations, which is consistent with our previous findings [18]. (2) PK/PD based optimizations suggest increased opioid administration to improve post-operative emergence and analgesia, which is consistent with Liu et al. [15]. (3) Administering fentanyl during the entire intraoperative procedure amplifies it's effect as an transition opioid as compared to when it is only administered close to the end of surgery as a single set of boluses.

In conclusion, use of PK/PD based models can theoretically enable clinicians to prolong post-operative analgesia with minimal impact on time to emergence by increasing fentanyl and decreasing remifentanil administrations.

Table 3 Predicted time to emergence, duration of analgesia, and ventilatory depression for actual dosing data and the algorithm recommended dosing regimens

	Actual dosing	Clinical scenario 1 dosing	Clinical scenario 2 dosing	F ratio	p value
Primary outcome measures					
Predicted time to emergence (min)	6.2 [4.3–7.2]	6.5 [5.0–7.3]	7.7 [6.7–9.2]	54.4	< 0.0001
Predicted duration of analgesia (min)	21.2 [16.3–25.8]	27.2 [23.5–29.8]	47.2 [31.8–89.7]	50.3	< 0.0001
Secondary outcome measures					
Predicted duration of intolerable ventilatory depression (min)	7.5 [5.3–9.7]	5.5 [3.8–7.3]	12.7 [9.0–15.7]	9.5	0.0003
Combined predicted time to emergence and duration of intolerable ventilatory depression (min)	7.7 [5.3–9.7]	7.2 [5.8–9.0]	12.7 [9.7–15.7]	9.5	0.0002

Data presented as median [inter quartiles]

Clinical scenario 1 prolonged analgesia with a minimal change in the time to emergence. Clinical scenario 2 prolonged analgesia permitting a slight delay in the time to emergence

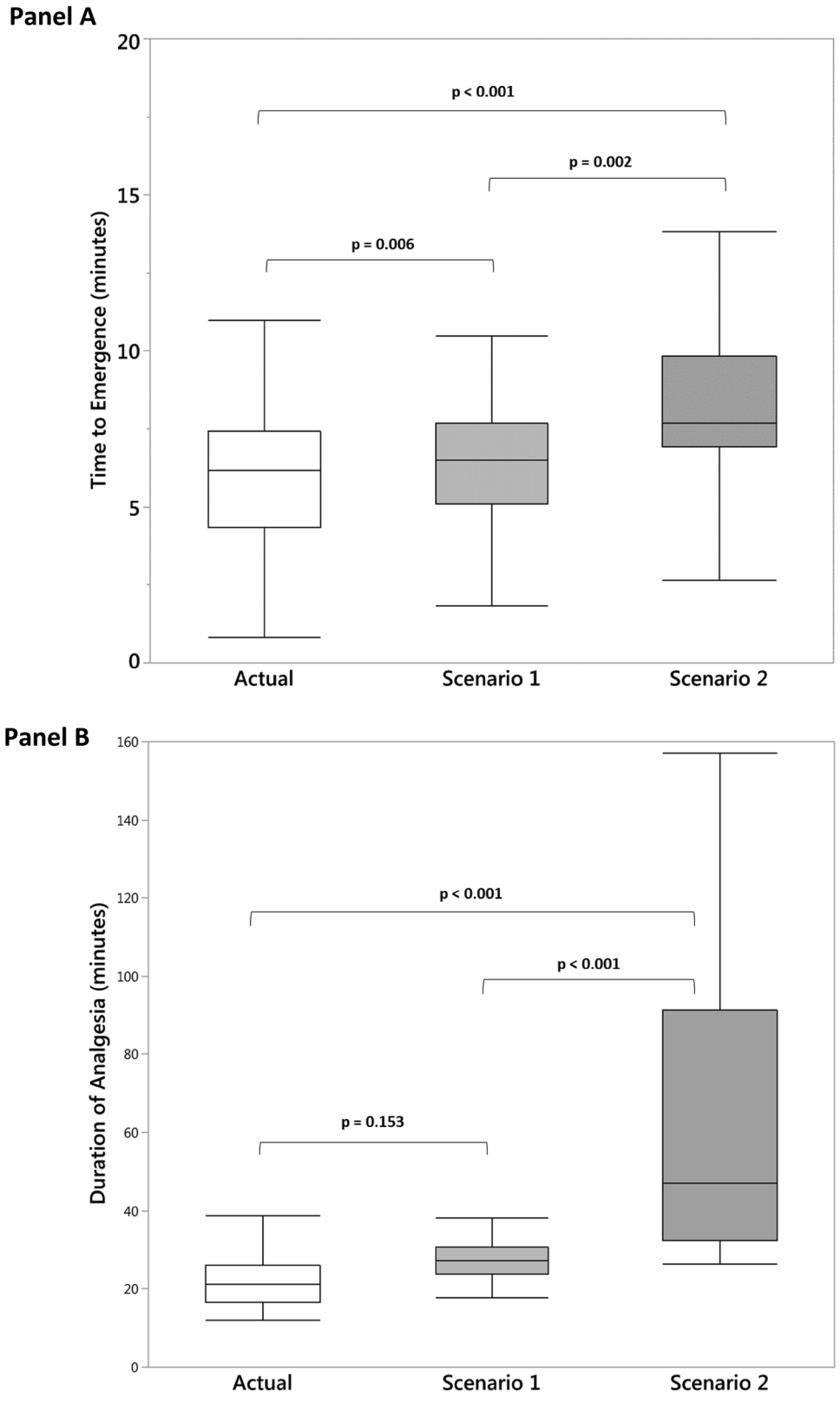


Fig. 6 Median differences in time to emergence (Panel **a**) and duration of postoperative analgesia (Panel **b**) among dosing regimens

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