ISAP 29th Annual Meeting

Pharmacological Considerations of ERAS Protocols

2020 Syllabus

Friday, October 2nd, 2020
0830–1645 U.S. Eastern Time

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2020 | www.isaponline.org

29th Annual Virtual Meeting

Mission Statement

The International Society for Anaesthetic Pharmacology (ISAP) is a nonprofit organization with an international membership, which is dedicated to teaching and research about clinical pharmacology in anesthesia, with particular reference to anesthetic drugs.

Accreditation Information

Workshop Target Audience: This program is designed for an international audience of general anesthesiologists, residents in anesthesia and specialty physicians who want to learn about practical applicable pharmacological knowledge for an improved predictability of anesthetic effect.

Objectives of the Workshop: After attending this interactive workshop you should be able to:

1. Explain the uses and potential benefits of depth of anesthesia monitors on patient outcomes post-surgery
2. Discuss the pros/cons of using opioids as part of a balanced anesthetic
3. Describe how the use of or omission of opioids impacts patient recovery

Practice Gaps Workshop

- For commonly used anesthetic drugs, there are useful pharmacokinetic-dynamic models available that relate a dose to several desired effects. However, it remains a challenge to apply the provided evidence in practice.
- Target controlled infusion pumps that titrate towards effect-site concentration are currently not available for clinical use in the USA. Alternative solutions to cope with this limitation are less well known.
- It is not common knowledge how a prediction of anesthetic effect derived from a population can be made valuable for individual patients also.

Program Target Audience: This program is designed for an international audience of general anesthesiologists, and anesthesiologists with a special interest in clinical pharmacology and technology.

Objectives of the Program: After attending this program you should be able to:

1. Understand the uses and potential benefits of using depth of anesthesia monitors on patient outcomes post-surgery
2. Discuss the pros/cons of using opioids as part of a balanced anesthetic
3. Understand how the use of or omission of opioids impacts patient recovery
4. Describe the causes of post-operative delirium and understand which medications may potentiate this outcome

Practice Gaps Program

- Enhanced recovery after surgery guidelines have included opioid-sparing techniques. A better understanding of how opioid minimization benefits patient recovery, if at all, is prudent.
- Improved anesthetic outcomes may be achieved through depth of anesthesia monitoring.
- A better understanding of how to identify patients at risk for post-operative delirium and the effects of anesthesia on post-operative delirium is necessary.
- Avoidance of specific medications may be justified for patients at risk for post-operative delirium.

Satisfactory Completion: Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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Physicians: Amedco LLC designates this live virtual activity for a maximum of 8.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Acknowledgement of In-Kind Commercial Support

No in-kind commercial support was received for this educational activity.

29th Annual Virtual Meeting

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Hugo	Vereecke	Masimo:Research Grant Site Principal Investigator / Draeger:Research Grant Site Principal Investigator

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1. **Go to http://isap.cmecertificateonline.com**
2. **Click on the "ISAP 29th Virtual Annual Meeting 2020" link.**
3. **Evaluate the meeting.**
4. **Print all pages of your certificate for your records.**

Questions? Email Certificate@AmedcoEmail.com

Participant Notification

We acknowledge the potential presence of limitations on information, including, but not limited to: data that represents ongoing research; interim analysis; preliminary data; unsupported opinion; or approaches to care that, while supported by some research studies, do not represent the only opinion or approach to care supported by research.

29th Annual Meeting Schedule

0830 – 1030..... **Interactive ISAP Workshop 2020**

Practical Concepts of Anesthetic Pharmacology for The Benefit of Your Patient.
A practical course that will improve your skills for anesthetic drug administration.

This two-hour interactive workshop is intended for residents and consultants in anesthesia who would like to learn about methods of drug titration that can result in a more controlled condition of the patient, both during induction, maintenance and recovery of anesthesia. Two experienced workshop presenters Steve Shafer, MD, Stanford, USA, and Hugo Vereecke, MD, PhD, Groningen, The Netherlands, will share their knowledge and discuss basic concepts of anesthetic pharmacology that can be applied easily in clinical practice to the benefit of your patient.

The learning objective: *To obtain skills for adapting drug titration towards available pharmacological evidence.*

Workshop Concept: *By interacting with the audience, practical problems that may occur in clinical practice will be shared and discussed. After this workshop the attendants will have learned the importance of concepts such as "time to peak effect" and "context sensitive halftime" and how to apply these in clinical practice. Technological solutions that assist in individualizing the drug titration during a balanced anesthesia will be discussed. The concept of "effect-site concentration" will be used and explained as an easy tool to understand the time course of drug effect related to different titration techniques.*

Workshop presenters: *Steve Shafer, MD, Stanford University, CA, USA & Hugo Vereecke, MD, PhD, University of Groningen, The Netherlands*

1030 – 1230..... **Session 1 - Tailoring Your Anesthetic to Promote Enhanced Recovery**

1030 – 1130..... **Depth of Anesthesia and Adverse Outcomes After Major Surgery**
Kate Leslie, MD, FANZCA

1130 – 1230..... **ERAS & Opioids: The Good, The Bad, & The Ugly**
Engy T. Said, MD & Rodney A. Gabriel, MD, MAS

1230 – 1430..... **Session 2 - Strategies to Avoid Post-Operative Delirium**

1230 – 1330..... **Perioperative Strategies to Prevent Postoperative Delirium**
Lis Evered, BSc, PhD

1330 – 1430..... **Best Practices in Prevention of Postoperative Delirium: Avoidance of Beers Criteria Medications**
Anne Donovan, MD

1430 – 1600..... **Moderated Poster Session**

1600 – 1645..... **Keynote Speaker & Lifetime Achievement Awardee**
The Impact of Clinical Pharmacology on My Academic Career
Tom Krejcie, MD

1645 – 1730..... **Virtual Reception**

Planning Committee

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Abstract Table of Contents

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Ketamine Produces a Long-lasting Enhancement of CA1 Neuron Excitability

Presenting Author: Grace N Jang, MPH[1]
Co-Author: M Bruce MacIver, MSc, PhD[1]

[1]Department of Anesthesiology, Perioperative and Pain Medicine; Stanford University

Introduction: Ketamine has recently been shown to improve major depressive disorder in patients who are unresponsive to other forms of treatment. The antidepressant effect occurs rapidly, often following a single exposure, and can outlast the presence of the drug for days or even weeks. Current evidence suggests that the mechanisms for this effect involve actions in addition to NMDA receptor antagonism. Little is known about other molecular targets for ketamine. The present study examined the effects of ketamine on synaptic transmission at glutamate and GABA synapses to determine whether changes in activity at these synapses contribute to the long-lasting effects produced by this drug.

Methods: All procedures were approved by the Stanford University Animal Use Committee. Male C57BL/6J mice weighing between 25-30 grams were used to prepare 400 µM thick coronal brain slices. We studied the effects of ketamine and its major metabolites (2R, 6R & 2S, 6S)-hydroxynorketamine by electrically stimulating Shaffer-collateral axons while recording evoked responses from CA1 pyramidal neurons. We also studied GABA inhibitory responses using a paired-pulse paradigm.

Results: Concentration-dependent effects were observed at clinical concentrations (10 µM for antidepressant and 350 µM for anesthetic). Ketamine produced three effects: 1) an acute depression of population spike amplitudes, 2) an enhancement of GABA-mediated inhibition, and 3) a long-lasting increase in population spike amplitudes. The long-lasting increase in amplitudes was observed following drug washout and lasted for up to 4 hours (longest duration of recording). This increase was not produced by any anesthetics we have previously studied (halothane, isoflurane, desflurane, sevoflurane, ethanol, pentobarbital, phenobarbital, thiopental, propofol, dexmedetomidine, or urethane). Ketamine's effects were mimicked by its primary metabolites and by the NMDA receptor channel blocker, MK-801. However, these effects were only partially mimicked by the NMDA receptor antagonist, APV and by a broad spectrum potassium channel blocker, TEA. A long-lasting effect was not observed for EPSP responses, indicating a postsynaptic site for ketamine's action.

Conclusions: Our results agree with previous studies showing that ketamine produces an acute depression of population spike amplitudes with an increase in GABA-mediated inhibition. This is the first report to demonstrate a long-lasting increase in excitability following washout of ketamine from brain slices. The increase in excitability following washout was also seen with MK-801 but only partially evident with APV, demonstrating the importance of channel block downstream of NMDA receptors. Additionally, the results with TEA indicate a potential for potassium channel block in ketamine's long-lasting effect. We suggest that the long-lasting effect produced following washout of ketamine could be related to the long-lasting antidepressant effects produced by ketamine and its metabolites.

Using a Bayesian Approach to Estimate Chronic and Acute Cannabis Consumption

Presenting Author: Thomas K. Henthorn[1,]

Co-Authors: Azin Kheirandish Pishkenari[1] and Cristina Sempio[1]

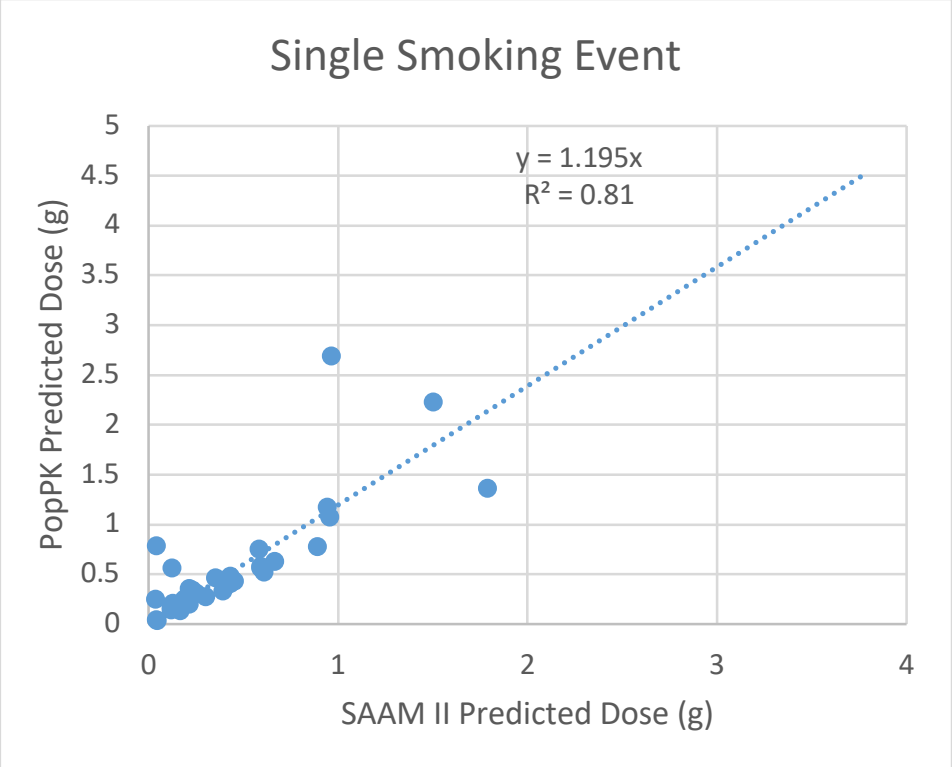
[1]Anesthesiology, University of Colorado, Aurora, CO

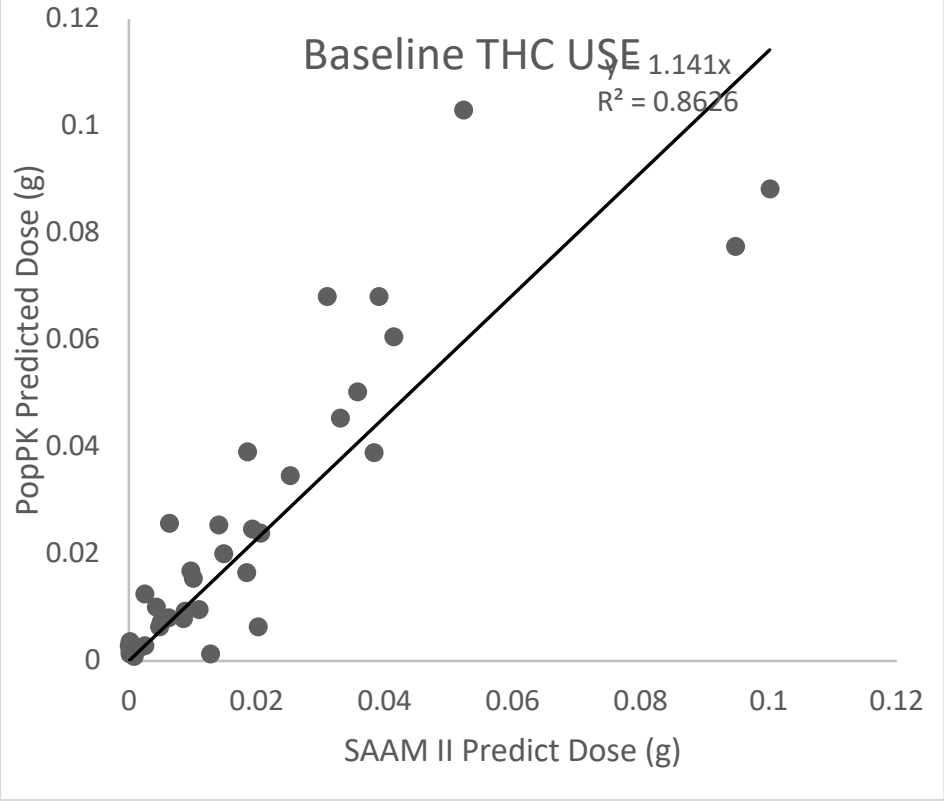
Introduction/Background: Cannabis for medicinal and recreational use is widespread and increasing. We have developed a popPK model of THC and two of its metabolites from Phase 1-like THC clinical trial studies. We previously used this popPK model to analyze THC and metabolite concentration versus time data from regular users of cannabis in Colorado in order to estimate the amount each individual used on both a daily basis (based on a single baseline blood sample) and smoked in a single an 'at home' episode that was not witnessed by investigators. These popPK-derived 'dose' estimates were statistically significantly correlated to detailed cannabis use questionnaire results at baseline and the weighed cannabis burned amount 'at home'. In order to interpret single or serial blood samples in clinical, forensic, or athletic event settings in an individual, a Bayesian prediction approach is needed. We hypothesized that estimates of daily and single cannabis use estimates obtained in one individual at a time, from THC and metabolite concentration data using a Bayesian approach, would be highly correlated to those obtained from full popPK modeling.

Methods: Thirty-seven regular users of cannabis from a larger study involving psychomotor testing were selected on the basis of indicating smoking as their primary method of cannabis consumption. Blood samples were obtained at recruitment, in a mobile lab immediately before smoking in their home, upon returning to the mobile lab and then again one hour later for analysis of THC/metabolites by LC-MS/MS. These data were analyzed with the Bayesian prior from our previous Phase 1-like popPK analysis (Pheonix NMLE, 8.1, Certara, Princeton, NJ). The same Bayesian prior estimates were used for fitting of each individual's data using SAAM2's Bayesian module. The individual fitting results were compared to the population posthoc values provided by Phoenix NLME results.

Results: There was a statistically significant correlation between the estimated THC baseline 'steady-state' cannabis usage determined with a population approach and with Bayesian forecasting approach utilizing just one individual's data ($r^2 = 0.73$, $p<0.01$) with a slope of 1.14. Additionally, there was a statistically significant correlation between the estimated THC consumed on a one-time smoking event ($r^2 = 0.63$, $p<0.01$) with a slope of 1.19.

Conclusions: The current study indicates that daily and single event cannabis usage can be estimated with plasma THC and metabolite concentration data from a single individual using Bayesian forecasting principles. Results are nearly identical to those obtained performing a popPK analysis of the data from all 37 individuals. There was a slight tendency for the individual Bayesian fits to under-predict doses compared to the popPK approach. While these results suggest that a well-characterized popPK model of THC and metabolites can be used to interpret observational or naturalistic concentration results, more robust popPK models of larger populations with the inclusion of covariates would likely improve accuracy and relevance.


Single Smoking Event
y = 1.195x
R² = 0.81
PopPK Predicted Dose (g)
SAAM II Predicted Dose (g)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
0
1
2
3
4


Baseline THC USE
y = 1.141x
R² = 0.8626
PopPK Predicted Dose (g)
SAAM II Predict Dose (g)
0
0.02
0.04
0.06
0.08
0.1
0.12

Substituted Cysteine Modification and Protection with Alkyl-MTS Reagents Estimates Etomidate-to-Residue Distances in $GABA_A$ Receptors.

Presenting Author: Stuart A. Forman
Co-Authors: Ryan Fantasia
Dept. of Anesthesia Critical Care & Pain Medicine, Massachusetts General Hospital, Boston, MA 02114, USA.

Introduction: Etomidate (ETO) acts at transmembrane β+/α- interfaces of $GABA_A$ receptors. Amino acid residues lining the ETO site, including β3M286, were identified through photolabeling and Substituted Cysteine Modification and Protection (SCAMP) methods. The SCAMP studies used 9 Å long, p-chloromercuribenzene sulfonate (pCMBS). We hypothesized that SCAMP using a series of n-alkyl-methanethiosulfonate (alkyl-MTS) reagents could provide more precise information about the distance between ETO and nearby amino acid residues. We tested this strategy in α1β3M286Cγ2L $GABA_A$ receptors.
Methods: Messenger RNA mixtures encoding α1β3M286Cγ2L $GABA_A$ receptor subunits (1:1:5 ratio) were injected into *Xenopus* oocytes, which were used in two-electrode voltage-clamp electrophysiologic experiments (20 °C; Vm = -50 mV) 18 to 48 hours later. Covalent modification by alkyl-MTS reagents at β3M286C residues was measured as changes in both the low:high GABA current response ratio [10 μM GABA (~ EC2-5) vs. 10 mM GABA] and ETO enhancement ratio [10 μM GABA + 10 μM ETO vs. 10 μM GABA]. Currents were measured in duplicate both before and after oocyte exposure to alkyl-MTS reagents + 3 mM GABA for 30 s, using 3 mM GABA alone as a control exposure. Averaged results after modification were normalized to pre-exposure average results in the same oocyte. Alkyl-MTS reagents that produced statistically significant and concentration-dependent changes in low:high GABA response ratios when compared to were further studied to determine if modification effects were altered by adding 300 μM ETO during alkyl-MTS + 3 mM GABA exposure. We inferred that ETO sterically interacted with the MTS reagent if significant inhibition of modification effects were found. Comparisons were based on Student's t-tests with $n \geq 5$ oocytes per condition.
Results: Alkyl-MTS reagents produced no persistent effects in wild-type α1β3γ2L $GABA_A$ receptors. In α1β3M286Cγ2L receptors, low:high GABA response ratios were unaffected by methyl-MTS or ethyl-MTS at up to 1 mM. Propyl-MTS, butyl-MTS, hexyl-MTS, octyl-MTS, and decyl-MTS all enhanced low:high GABA response ratios ($P = 0.0042$, 0.0006, <0.0001, 0.0008, 0.0034 respectively). ETO enhancement was unaffected by methyl-MTS, increased by ethyl-MTS ($P = 0.0247$), and reduced by larger alkyl-MTS reagents. ETO at 300 μM reduced the effects of exposure to propyl-MTS, butyl-MTS, hexyl-MTS, and octyl-MTS ($P= 0.0032$, 0.0011, <0.0001, 0.0219 respectively).
Conclusion:
We observed a 'cut on' for β3M286C modification effects on both GABA and ETO sensitivity between ethyl-MTS and propyl-MTS, and also found that receptor-bound ETO blocked modification by propyl-MTS and larger reagents. Accounting for the different side-chain lengths of methionine and cysteine, our results indicate that ETO is located 1.7 to 3.0 Å from β3M286 (Fig. 1). SCAMP with alkyl-MTS reagents may be more widely useful as a 'molecular ruler' to assess distances between ETO and other anesthetics and nearby residues in $GABA_A$ receptors.

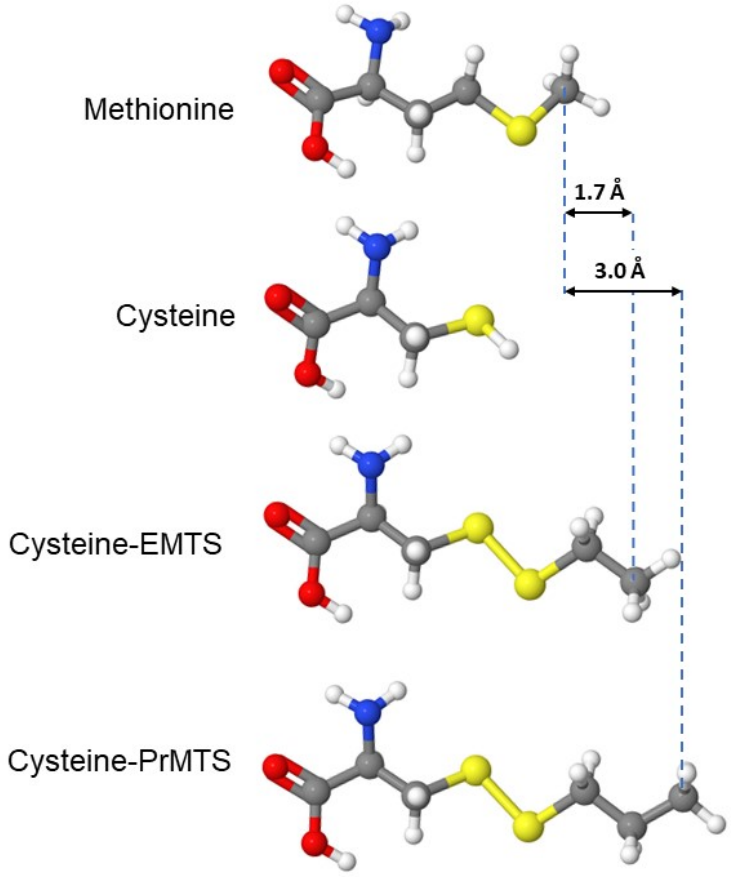


Fig 1. Interpretation of alkyl-MTS effects on α1β3M286Cγ2L $GABA_A$Rs. Modification with reagents longer than ethyl-MTS produce effects on GABA and ETO sensitivity that are inhibited when ETO is present during exposure, suggesting overlap with receptor-bound ETO.

Title: Monitoring the risk for a "valley of inadequate anesthesia" using bispectral index and the noxious stimulation response index during different inflow speeds of sevoflurane.

Authors: Mira Van Thielen MD[1 2], Rik Carette MD[1], Jan F.A. Hendrickx MD, PhD[1 2], Andre M. De Wolf MD, PhD[3], Hugo E.M. Vereecke MD, PhD[4 5]
Affilliations: [1] OLV Hospital, Aalst, Belgium; [2] Ghent University, Ghent, Belgium; [3] Northwestern University, Chicago, USA; [4] AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium; [5] University Medical Center Groningen and University of Groningen, Groningen, The Netherlands

Abstract

Introduction: The "valley of inadequate anesthesia" refers to an increased risk for awareness, movement or hemodynamic instability evoked by an insufficient inflow of volatile agents to compensate for the gradual elimination of intravenously administered boluses of induction agents. The combined drug effects of volatile and intravenous drugs should ensure a sufficient hypnotic drug effect and immobility (as respectively quantified by bispectral index (BIS, Medtronic) and the noxious stimulation response index (NSRI, Dräger)), while maintaining stability in arterial blood pressure (ABP) and heart rate (HR). NSRI is a derivative of the probability of tolerance of laryngoscopy, as estimated by Hannivoort et al. for most combinations of propofol, opioids and volatile agents.[1] NSRI of 20 equals an estimated probability of immobility in response to laryngoscopy of 90%. We compare the time course of BIS, NSRI, ABP and HR after a bolus of propofol and sufentanil, followed by three different inflow speeds of sevoflurane. We hypothesize that BIS and NSRI should stay below 60 and 20, respectively, at all times between the start of sevoflurane and reaching a target of 1.0 MAC. We also compare ABP and HR between groups.

Methods: 33 ASA score I-III patients (age range: 27-86 years; BMI range 22-34 kg/m^2) presenting for abdominal surgery received sufentanil (0.2 µg/kg) and propofol (1 or 2 mg/kg, depending on age) followed by intubation of the trachea, 2.5 min after loss of responsiveness and rocuronium (0.6 mg/kg). Sevoflurane was administered (after randomization) in a 'slow'(n = 9), 'medium'(n = 8), and 'fast'(n = 9) group; defined by a time constant of respectively 10.9, 5.7, and 2.6 min wash-in time towards 1.0 MAC. These inflow speeds are similar to those used in a commercialized automatic controller of the inflow of volatile agents (Flow-I, Maquet). BIS and NSRI were blinded to the anesthesiologist. For all measures, the 95% confidence interval (CI 95%) of the difference of means was calculated at one minute intervals between minutes 0 to 25 after propofol ($p < 0.05$ if zero is outside 95% CI). An escape bolus of sufentanil (0.1 µg/kg) was allowed per protocol (and included in the NSRI calculations) to counter movement, tachycardia or hypertension indicating insufficient anesthesia at any time.

Results and discussion: Extra sufentanil was needed in all groups, for movement (1 in slow, 1 in medium, 1 in fast), for tachycardia (1 in slow, 1 in medium and 1 in fast), and for hypertension (3 in medium, 2 in fast). Figure 1 shows the time course of BIS, NSRI, HR and MAP. All groups included cases with BIS > 60 and/or NSRI > 20 (n in slow > medium > fast). High BIS and NSRI were not always consistent.

Figure 2 shows similar BIS and NSRI during the first 8 minutes in all groups, confirming equipotency for these measures till the start of sevoflurane. Mean NSRI differs between slow and medium, slow and fast and medium and fast (respectively from minute 10 to 18, 10 to 20 and 10 to 14) evoked by the deliberate differences in inflow speed of sevoflurane. Mean BIS differs between slow and medium and slow and fast (respectively from minute 15 to 16 and 11 to 24). Heart rate and blood pressure did not differ between groups. A Brice questionnaire found no cases of explicit recall.

Conclusion: After a bolus dose of propofol, sufentanil, and rocuronium, both BIS>60 and NSRI>20 warn the anesthesiologist for an increased risk of a "valley of inadequate anesthesia". ABP and HR don't identify differences in drug potency between groups. A higher initial dose of sufentanil (e.g. 0,3 µg/kg) might reduce the need for escape treatment.

Reference

1. Hannivoort LN, et al., Br J Anaesth. 2016 May;116(5):624-31.

Figure 1: Raw data:
Time course of individually measured bispectral Index (BIS), noxious stimulation response index (NSRI), heart rate and mean arterial blood pressure in all groups. Each black line is data from a single patient. The dotted lines indicate the thresholds for BIS (40 and 60) and for NSRI (20).

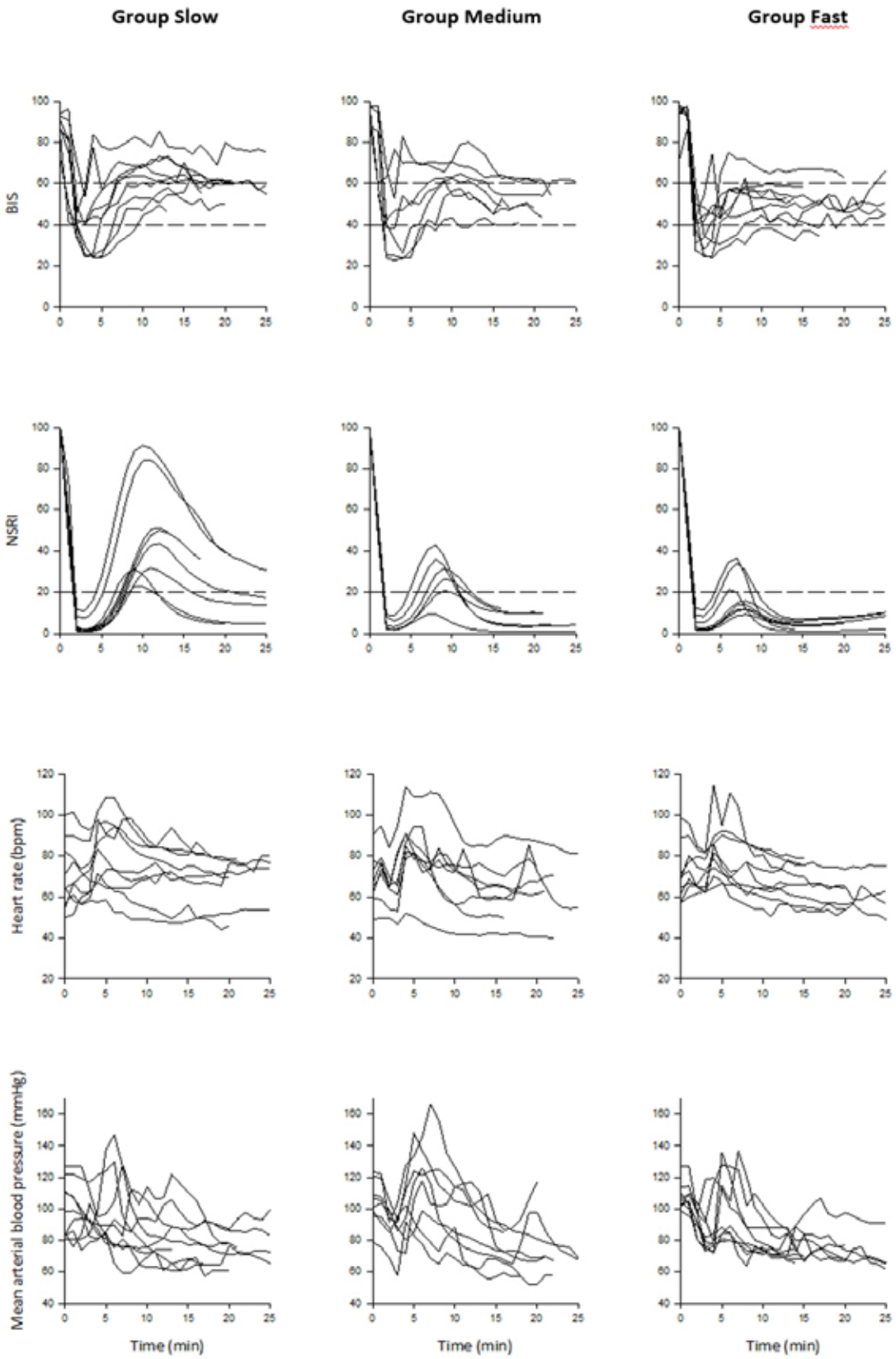
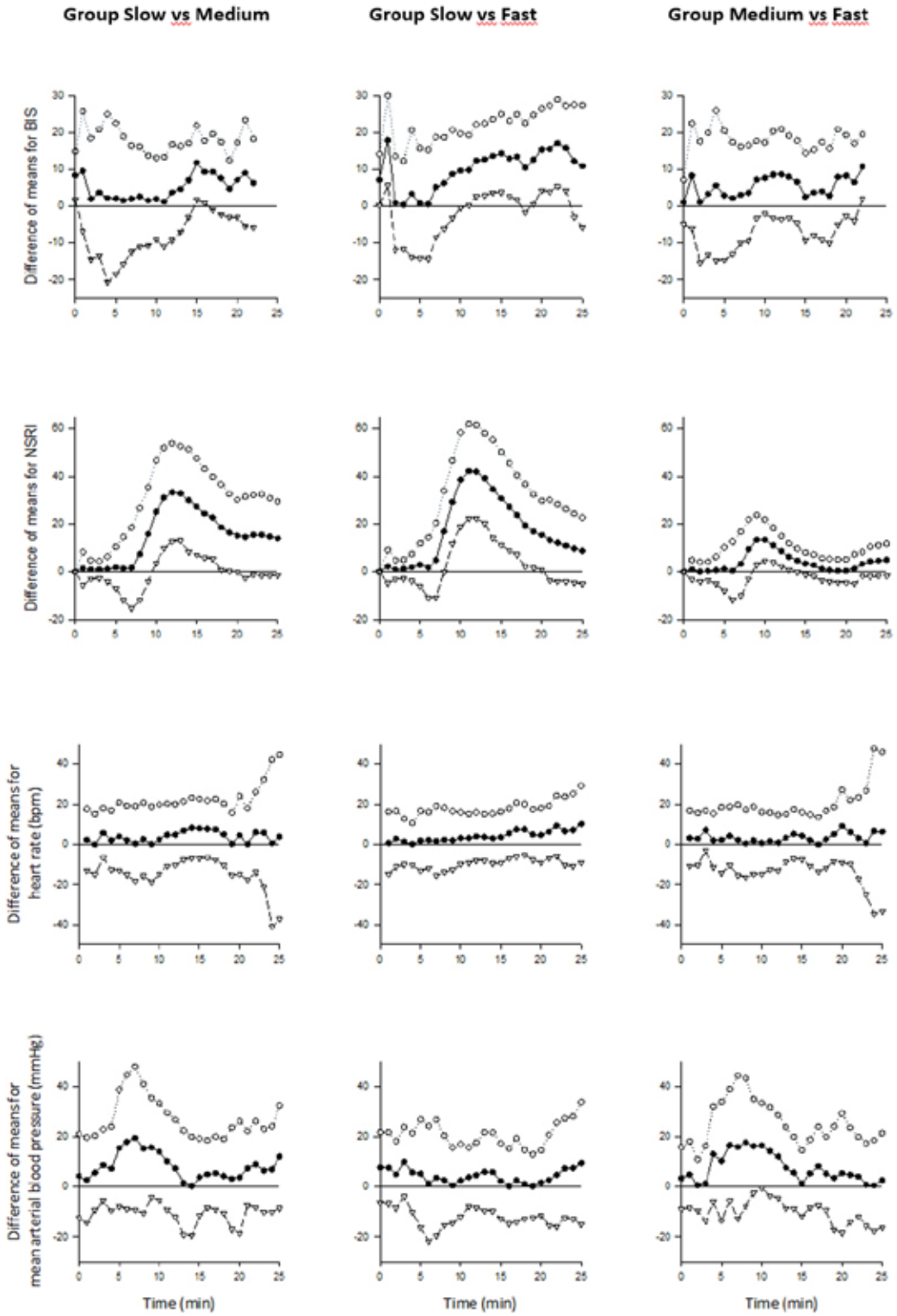


Figure 2: Difference of means between groups with 95% confidence intervals at one minute intervals. Bispectral index (BIS), noxious stimulation response index (NSRI). Black dots are the differences of the means between the groups. The light dots and the triangles are respectively the upper and lower margins of the 95% confidence interval. P < 0.05 when the zero line is outside of the 95% confidence interval.



A pharmacoepidemiological method for assessing clinician performance during esophagogastroduodenoscopy procedures sedated with propofol

Jeff E Mandel MD MS

Mandel Anesthesia Innovations LLC

Media, PA

Background: Despite the explosive growth of endoscopic sedation, little has been done to understand how clinicians control propofol during these procedures. Anesthesia providers must balance the desire for rapid induction and avoidance of over sedation, evolving a strategy that is optimal with respect to the expectations of the endoscopists. While multiple pharmacokinetic models have been delineated for propofol, a data-driven approach to assessing the facility of a clinician at the task of propofol administration has yet to emerge. Two objective measures for evaluating quality of control are proposed. The first considers adjustments to the initial plan. This is determined by considering what propofol delivery would have been had no changes been made from the initially recorded bolus and infusion. The cumulative absolute value of this difference (expressed in mg) is termed the adjustment dose. The second measure is the propofol trajectory error. At each time point, the cumulative propofol for each patient is ranked from 0 (lowest observed) to 1 (highest observed). The trajectory error is the standard deviation of the ranking over the procedure. If a particular patient is consistently at the 50th percentile for propofol delivery for the entire procedure, the tracking error is zero, however, if the patient is at the 34th percentile initially and at the 65^{6h} percentile 20 minutes later, the trajectory error is 0.26. The upper limit for trajectory error is

0.5. The trajectory error permits comparisons of propofol consumption in patients of differing ages and weights.

To make an aeronautical analogy, adjustment dose is how much we “fight the stick”, while trajectory error is how much we deviate from our filed flight plan.

Methods: Data was extracted from the Penn Data Analytics database for all esophagogastroduodenoscopy cases from Jan 2016 to December 2017; cases with only bolus delivery were excluded, leaving 13,503 cases. Patterns in choice of initial bolus and infusion rate were assessed. Timed delivery entries were converted to continuously sampled infusion rates. Scores for adjustment dose and trajectory error were determined for each of these cases.

Results: Median adjustment dose 26 mg (12 – 56); a histogram is presented in figure 1. Median trajectory error was 0.26 (0.23 – 0.28); a histogram is presented in figure 2. Correlations between the two measures and age or weight and were close to zero, as was the correlation between measures.

Conclusions: While there is considerable similarity in the initial bolus and infusion rates during endoscopic sedation, there is a larger diversity in adjustment dose and trajectory error. Further, these measures are minimally correlated with age and weight, or with each other, suggesting they are measuring properties of the controller, rather than the controlled, and that they are measuring distinct aspects of the control. These measures may prove useful in assessing the skill of anesthesia providers in delivering endoscopic sedation, or in assessing the performance of automated systems.

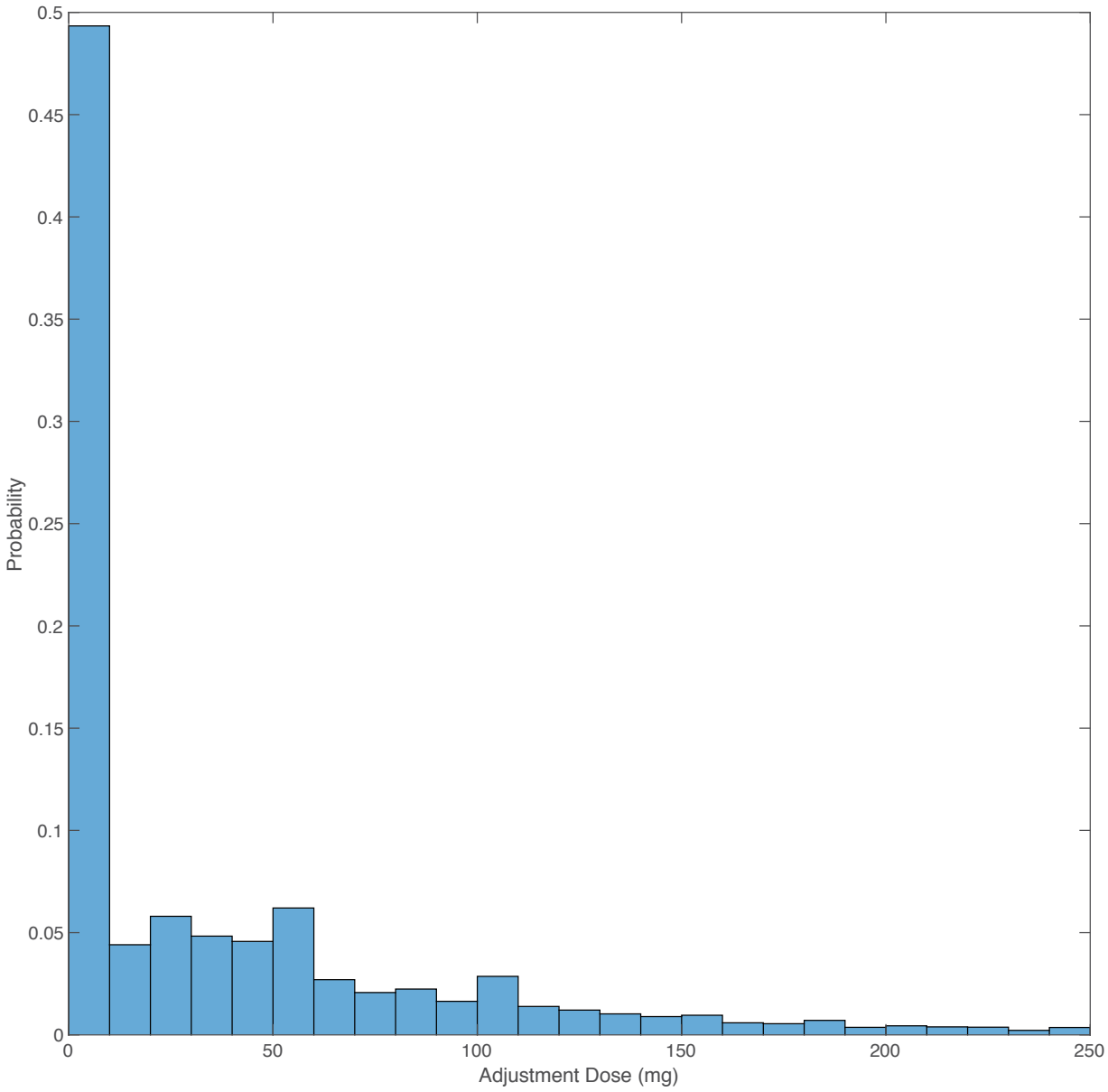

0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Probability
0
50
100
150
200
250
Adjustment Dose (mg)

Figure 1

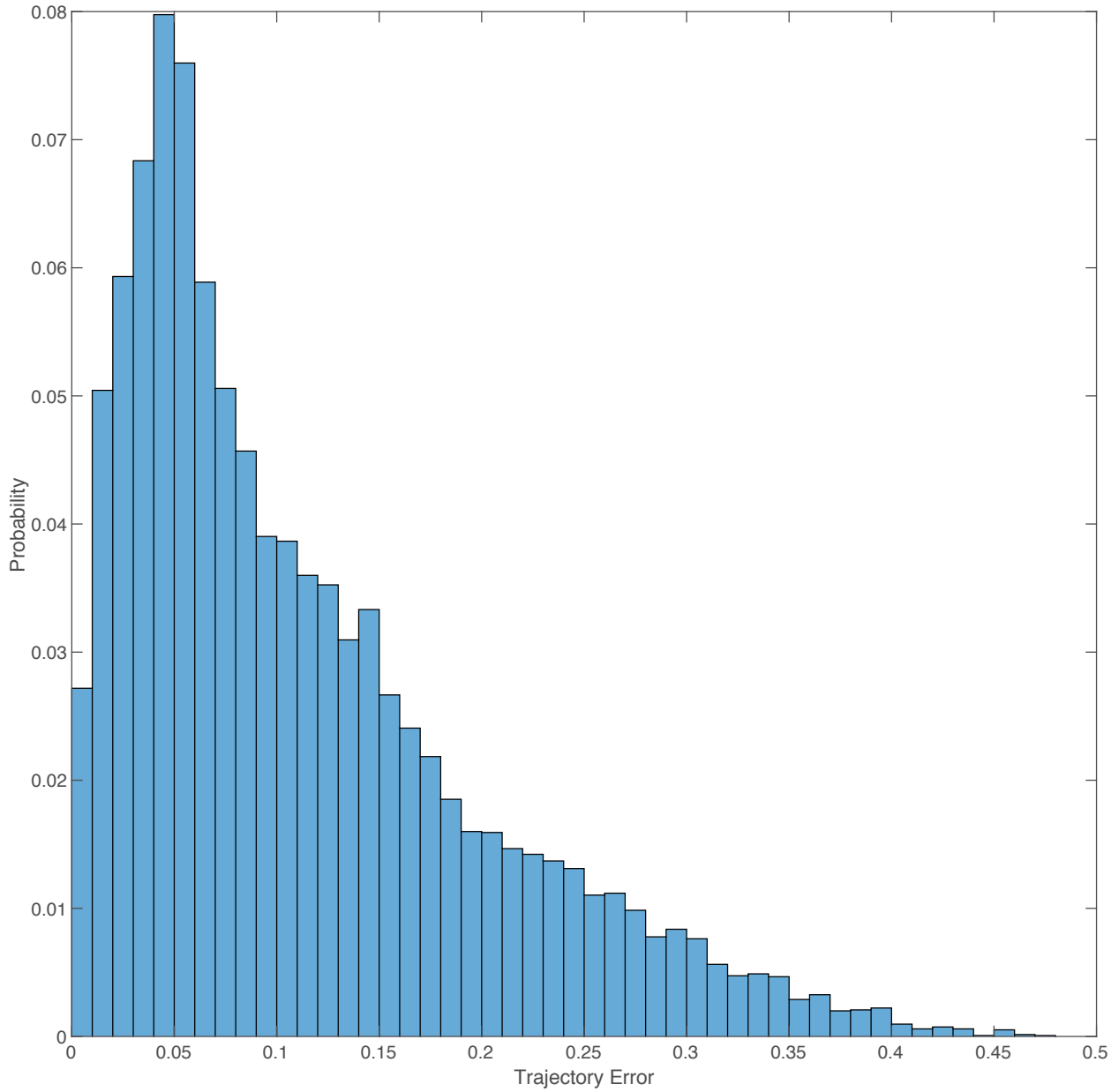

0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Probability
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Trajectory Error

Figure 2

A Pharmacoepidemilogic approach to propofol delivery during esophagogastroduodenoscopy

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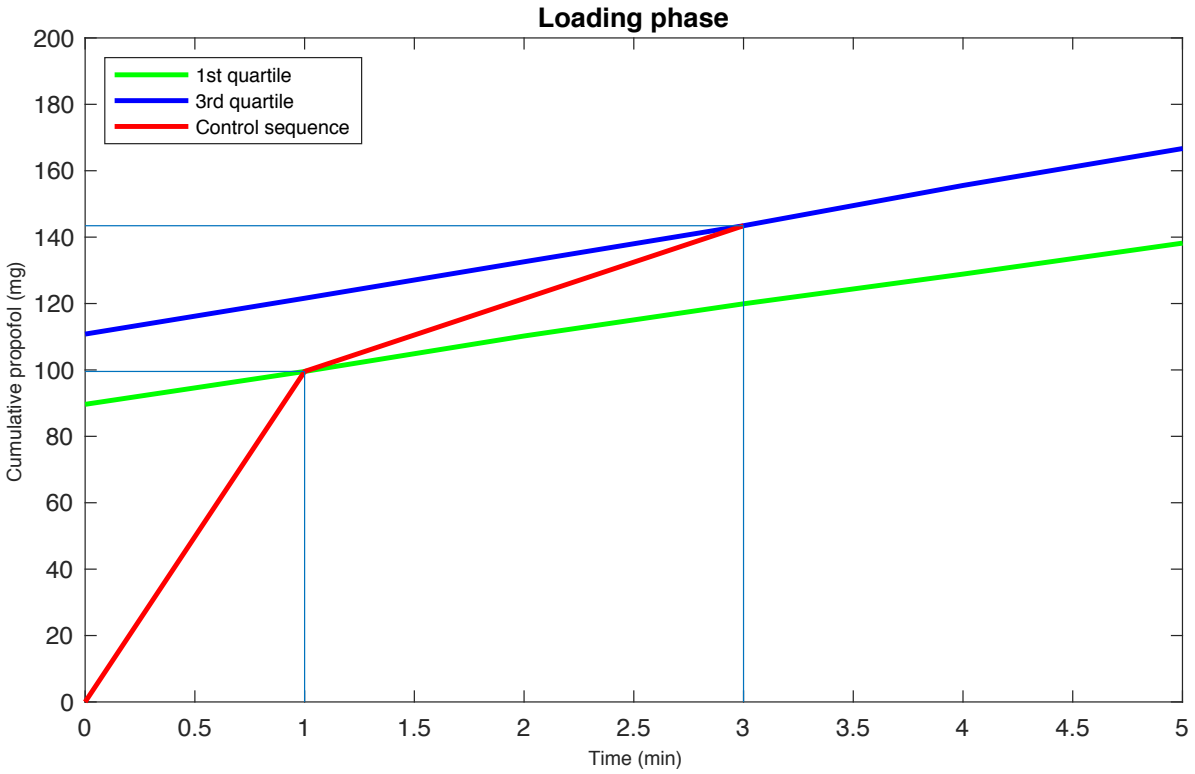
Background: Delivery of propofol for brief procedures such as esophagogastroduodenoscopy (EGD) is a commonly performed task which requires rapid assessment of patient sensitivity and adaptation of drug delivery to maintain appropriate sedation. While pharmacokinetic (PK) models may reduce the impact of covariates such as age or weight on drug effect, with a sufficiently large cohort a subcohort of patients of similar age and weight can be selected that will yield a lower error than that of a PK model. A control system that is based on such a pharmacoepidemilogic (PE) approach is described.

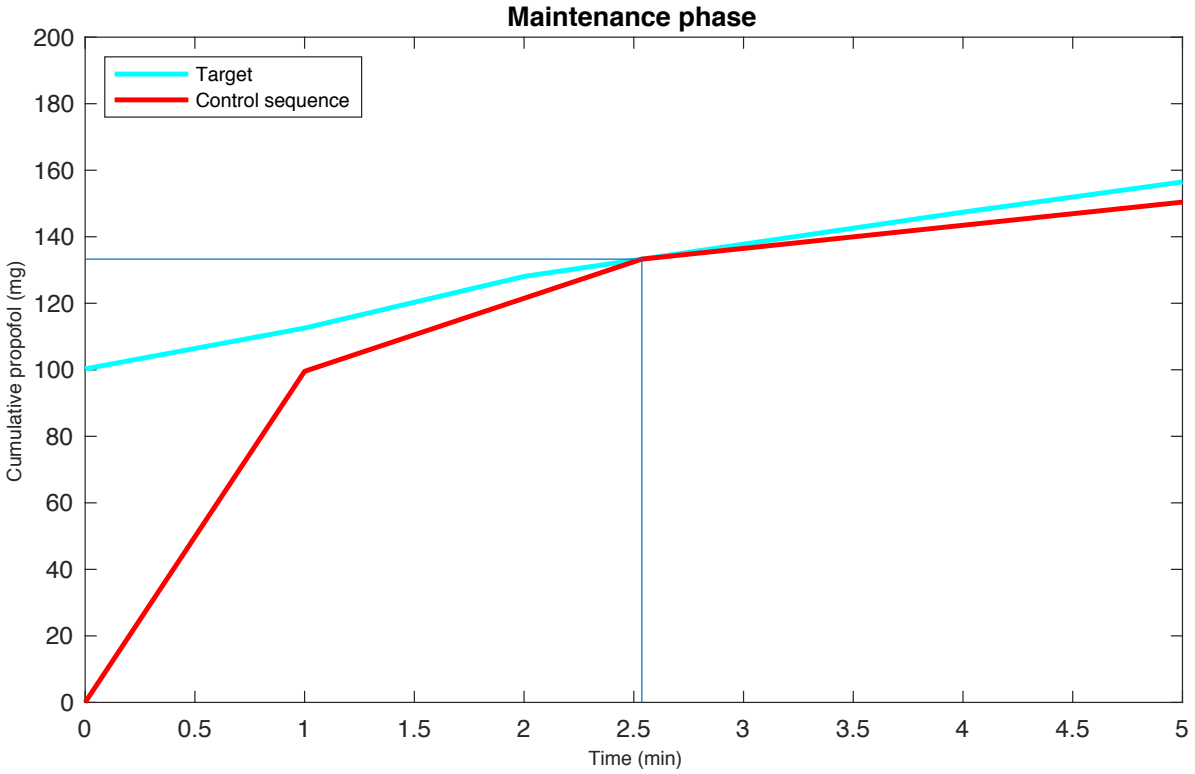
Methods: Data was extracted from the Penn Data Analytics database for all esophagogastroduodenoscopy cases from Jan 2016 to December 2017; cases with only bolus delivery were excluded, leaving 13,503 cases. Timed delivery entries were converted to continuously sampled infusion rates, and cumulative propofol administration determined at one-minute intervals. For any given patient, a subcohort of 100 patients is selected that most closely approximates the age and weight, and at each time interval the cumulative propofol ranked from lowest to highest. An infusion sequence (red) is determined that connects 3 points – 0 propofol at 0 minutes, the first quartile at 1 minute, and third quartile at 3 minutes. Note that the green and blue lines have non-zero y intercepts reflecting an initial bolus. This loading sequence is depicted in upper panel of the figure. The loading sequence is delivered until

adequate sedation is observed, the estimated ranking at that instant determined, and the control sequence updated to track the identified target, as depicted in the lower panel of the figure.

Results: Over the interquartile range of ages and weights, a subcohort of 100 patients can be formed with a maximum age range of 2 years and 2 kg.

Conclusions: PE control has several advantages over PK control. The control is based on actual observations during drug administration. As additional observations accrue, greater precision in covariates or additional covariates are possible. The observations can be specific to a particular locale. Implementation is simple, and can be performed with manual entry into a syringe pump. PE control will require clinical validation.


Loading phase
1st quartile
3rd quartile
Control sequence
Cumulative propofol (mg)
Time (min)
0
20
40
60
80
100
120
140
160
180
200
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5


Maintenance phase
Target
Control sequence
Cumulative propofol (mg)
Time (min)
0
20
40
60
80
100
120
140
160
180
200
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

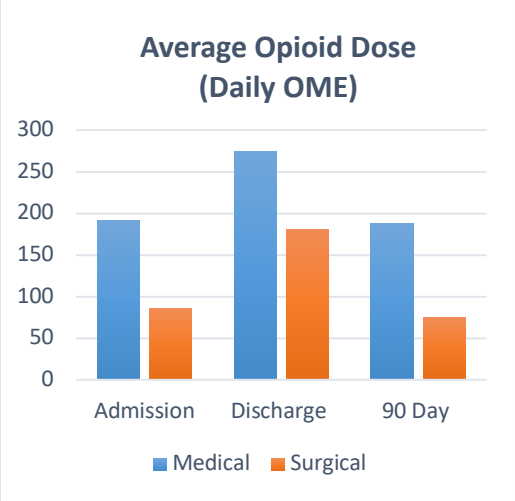
Ketamine Infusions for Pain Control in Acute Care: persistent opioid use analysis in medical vs surgical patient population

Tatyana Der, MD, Amanda Nelli, MD, Padma Gulur, MD

Introduction: The Opioid crisis has prompted the medical community to seek the use of non-opioid modalities to treat pain. Recent consensus guidelines on the use of IV ketamine in patients with acute pain support the use of these infusions for the treatment of their pain in acute care settings[1]. Studies on opioid sparing properties of ketamine infusions received during surgeries, for pain control in emergency departments, and during hospitalization for patients with vaso-occlusive crisis have shown promise[2-4]. At Duke University we have extensive use of Ketamine infusions for acute and acute on chronic pain on inpatient floors. We conducted a retrospective review of Ketamine infusions used to treat the pain during inpatient stays.

Methods: All adult patients who received ketamine infusion for pain from Jan-Dec 2017 were evaluated. 510 unique patients (both medical and surgical) were identified. The surgical group was defined as having any type of surgery in the OR, while procedures, such as tracheostomy placement or exchange, preformed bedside were not considered surgical admissions. 394 of 510 patients were classified as surgical and 116 of 510 patients as medical. Ketamine infusions were given to achieve desired level of pain control or until intolerable side effects necessitated to stop infusion. The decision to use Ketamine infusions was made by Acute Pain Service or Critical Care attending, and were managed in accordance with institutional guidelines. Persistent opioid use at discharge and 3 months was derived from available electronic medical records. The daily dose of opioids was calculated by using maximum prescribed daily dose, and reported in Oral Morphine Milligram Equivalent (MME).

Results: The average MME on admission for the medical group was 191.3 while the surgical group was 86.7. On discharge, the medical group average MME is 274 and the surgical group is 181.4. At 90-days after discharge, the average MME for the medical group is 188.8 and 75.4 for the surgical group. The medical group had a 30.2% increase in average MME from admission to discharge, and a 1.3% decrease in average MME at 90-days after discharge. The surgical group had a 52.2% increase in average MME from admission to discharge, however, they had a 13% decrease from admission to 90-days after discharge.



Conclusion: Our retrospective review of Ketamine infusions for pain control elucidated persistent use of opioids at and after discharge in both medical and surgical patient groups. The opioid use among the medical patients was significantly higher than the surgical group. While there is an expected increase in pain medications, particularly opioids, during the postoperative period, the significant increase in opioids on discharge in the medical group in unexpected. At 90 days after discharge, the surgical group did have a greater decrease in baseline opioid use, whereas the medical group was close to baseline opioid use.

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A Phase 2 Trial of Inhaled Nitrous Oxide for Treatment-Resistant Major Depression

Short Title: Nitrous Oxide and Treatment-Resistant Depression

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Abstract

Background: In a prior proof-of-concept study, a single inhalation of 50% nitrous oxide rapidly improved depressive symptoms in patients with treatment-resistant major depression. It is unknown, however, whether a lower concentration of 25% nitrous oxide provides similar efficacy while reducing the risk of adverse side effects and how long antidepressant effects last.

Methods: In this phase 2 clinical trial, 20 patients with severe treatment-resistant major depression were randomly assigned in a crossover fashion to receive a single 1-hour inhalation with (1) 50% nitrous oxide, (2) 25% nitrous oxide, or (3) placebo (air). Inhalation treatments were at least 4 weeks apart. Primary outcome was the change on the Hamilton Depression Rating Scale 21-item (HDRS-21).

Results: Nitrous oxide inhalation (25% and 50% combined) led to a significant improvement in depressive symptoms versus placebo (p=0.002), but we did not observe a statistically significant difference between 25% and 50% nitrous oxide (p=0.55). The estimated HDRS-21 differences between 25% and placebo were -1.01 points at 2 hours (p=.66), -1.82 points at 24 hours (p=.42), -5.05 points at 1 week (p=0.03), and -6.58 points at 2 weeks (p=0.004). The estimated differences between 50% and placebo were -0.88 points at 2 hours (p=.70), -1.88 points at 24 hours (p=.40), -2.81 points at 1 week (p=0.21), and -8.06 points at 2 weeks (p=0.003). Adverse events declined with dose: 43 (50% nitrous oxide), 11 (25% nitrous oxide), and 4 (placebo) (p=0.0003). None of the adverse events were serious and nearly all occurred during or immediately after inhalation and resolved within several hours.

Gas Man® simulation graphics improved for free teaching and learning

Presenting Author: James Philip[1,2]
Co-Authors: Myria Chen[3]

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Background/Introduction: Gas Man is a computer-based simulation that demonstrates inhalation anesthesia pharmacokinetics. The interactive Picture window allows users to carefully control the administration of anesthesia, just as they would clinically. With the Gas Man Graph, users can monitor the effect of anesthesia over time. They can also analyze and compare various situations utilizing the unique Overlay feature. To distinguish experiments within the Overlay, each anesthetic option is designated a different default color.

Methods: We used Gas Man's color capability to augment simulation visuals, increasing the ease with which users can differentiate experiments in the Overlay. If a set of exercises involved one anesthetic with varying parameters, each experiment's color was changed according to our new color scheme – the rainbow color code plus black as the first color (BROYGBV). The assigned color of each condition was based on chronological order of the exercises. If a simulation showed cost savings, it was colored green. To include Simulation Descriptions for every experiment, we created descriptions based on the Observations and Discussions in the Gas Man Workbook. The descriptions typically explained significant findings, concepts, and conditions of the exercise. We accessed the Simulation Description tab under "File" and inserted the description into the textbox. Lastly, we closely followed the Gas Man Workbook to simulate and save every exercise as a .gas file, with the above improvements implemented.

Results: We completed careful capture of all Gas Man Workbook exercises. We produced color accentuated educational paradigms and incorporated individualized exercise descriptions.

To compare the cost to reach 1 MAC in Exercises 14-1 and 14-2, we designated the color black for 14-1 and the color green for 14-2 (Figure 1). It is evident that the green curve has a much lower slope than the black curve, indicating that low fresh gas flow is more cost effective. The Simulation Description for Exercise 14-2 identifies exercise-specific elements and summarizes the main takeaway (Figure 2).

The simulations can be played back via the free Student Edition of the Gas Man program. These are posted on www.medmasimulations.org/education.
Register to get the Student Edition and have access to those simulations saved as .gas files.

Conclusions: We concluded that creating color-coded exercises and Simulation Descriptions enhanced the Gas Man experience for learners and teachers. The color scheme visually distinguishes experiments for easy comparison, and the Simulation Descriptions concisely convey key concepts and results for each exercise.

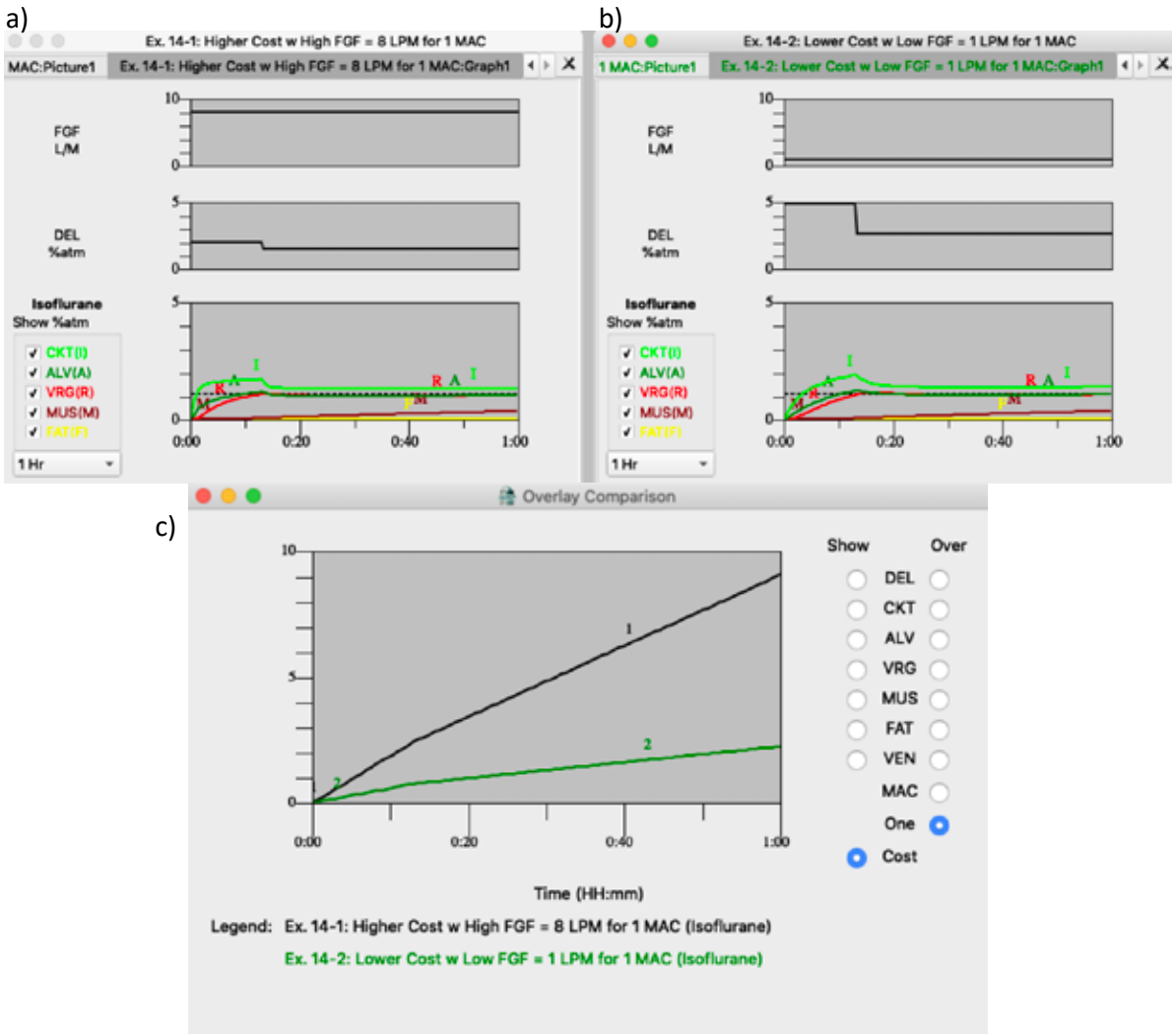

Figure 1. (a) Individual Graph of Exercise 14-1. (b) Individual Graph of Exercise 14-2. (c) Overlay of Gas Man® Exercises 14-1 and 14-2 comparing cost of isoflurane. The colors help differentiate between high FGF (black) and low FGF (green). To achieve and maintain 1 MAC, low FGF is much more cost effective.

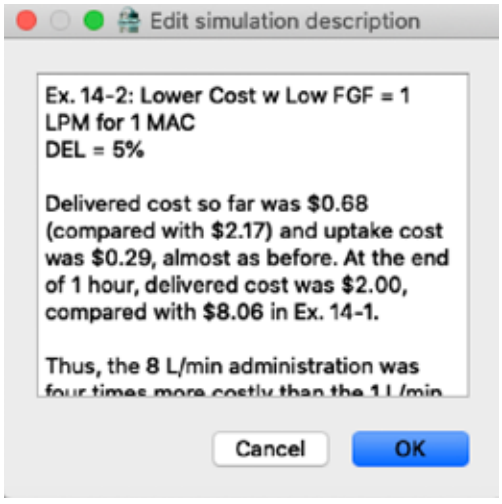

Figure 2. A portion of the Simulation Description for Exercise 14-2.

Effect of Psychological and Sociodemographic factors on Risk Perception of Coronavirus Infection (COVID-19)

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Introduction: Coronavirus disease (COVID -19) is a respiratory disease, which is caused by novel coronavirus. It is a source of mortality world- widely.

Method: Present study investigated the risk perception of coronavirus and effect of psychological and sociodemographic variables on perceived risk. Total 534 adult participants were included in the study. Three validated questionnaire (Risk Perception of Infectious Disease Questionnaire, General Self-Efficacy Scale and Personality Inventory questionnaire) were used to conduct the study.

Results: The results of the study showed that age, self-efficacy (F= 2.17, p= 0.03), education, and personality (F= 1.97, p=0.03) significantly influenced the risk perception. "Imagination" was the predictor of perceived "seriousness" (p=0.02), while "self-efficacy" was the predictor of "susceptibility" (p=0.001). The gender, status of employment, children aged <12 years and size of the household did not affect the risk perception for coronavirus.

Conclusion: To promote protective behavior among people , health care system need to know how people perceive risks of coronavirus infection and whether population will able to correctly use the information on COVID-19.

Effect of pedometer-based walking on depression, anxiety and insomnia among medical students

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Introduction: Insomnia, anxiety, and depression are some of the psychological symptoms reported by college going students, including those pursuing a medical degree. Physical activity helps students remain healthy and improves physical function.

Aim of the study: To evaluate the effect of a pedometer-based walking on anxiety, insomnia, and depression among medical students.

Material and Methods: In this study, 120 second year MBBS students were randomly assigned to two groups (n = 60 in each group). Anxiety, insomnia, and depression levels were assessed using the GHQ-28 and Beck questionnaires in the 4th, 8th, and 12th week of intervention. Participants of intervention group downloaded pedometer app in smart phones, and were asked to increase their steps by 500 per week. Data were analyzed using the independent t-test, chi-square, and repeated measures tests.

Results and Conclusion: Anxiety and insomnia level decreased in the 8th (4.7 ± 1.8 vs. 5.8 ± 3.1, $P = 0.01$) and 12th week (3.9 ± 1.4 vs. 6.2 ± 3.7, $P < 0.001$) in the intervention group, compared with the control group. The depression level decreased in the intervention group, compared with the control group, after 12 weeks (12.7 ± 4.8 vs. 19.6 ± 5.7, $P < 0.001$). The intervention group increased their step count from 78,357 steps per month in the first month, to 109,368 in the third month. This study showed the pedometer-based walking had a positive effect on depression, insomnia, and anxiety among medical students. A walking training program can be considered for students to manage anxiety insomnia and depression.