

Retrospective Study

Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience

Alexandra Shingina, George Ou, Oliver Takach, Sigrid Svarta, Ricky Kwok, Jessica Tong, Kieran Donaldson, Eric Lam, Robert Enns

Alexandra Shingina, Department of Gastroenterology, Faculty of Medicine, University of Toronto, Toronto General Hospital, Ontario M5G 2C4, Canada

George Ou, Sigrid Svarta, Department of Gastroenterology, Faculty of Medicine, University of British Columbia, Vancouver V5Z 1M9, Canada

Oliver Takach, Ricky Kwok, Jessica Tong, Kieran Donaldson, Eric Lam, Robert Enns, Division of Gastroenterology, Saint Paul Hospital, Vancouver V6Z 2K5, Canada

Author contributions: Shingina A and Enns R designed the project; Shingina A and Svarta S designed ethics proposal; Shingina A, Ou G, Svarta S, Kwok R, Donaldson K collected the data; Takach O and Lam E analyzed the data; Shingina A, Ou G, Svarta S, Lam E and Enns R wrote the manuscript.

Institutional review board statement: This study was reviewed and approved by the University of British Columbia - Providence Health Care Research Institute.

Informed consent statement: The informed consent is not applicable since this study is a retrospective review. All clinical data collected was dissociated from patient identifiers using a combination of alphanumeric characters in accordance to ethics board's requirements.

Conflict-of-interest statement: All authors of this paper have no relevant conflicts of interest to declare.

Data sharing statement: No data were created so no data are available.

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Manuscript source: Unsolicited manuscript

Correspondence to: Robert Enns, MD, Division of Gastroenterology, Saint Paul Hospital, 770-1190 Hornby Street, Vancouver V6Z 2K5, Canada. rob.enns@ubc.ca
Telephone: +1-604-6886332

Received: April 20, 2016

Peer-review started: April 20, 2016

First decision: June 12, 2016

Revised: July 25, 2016

Accepted: September 6, 2016

Article in press: September 8, 2016

Published online: December 16, 2016

Abstract**AIM**

To develop a prediction model aimed at identifying patients that may require higher than usual sedation doses during colonoscopy.

METHODS

A retrospective chart review on 5000 patients who underwent an outpatient colonoscopy at St. Paul's Hospital from 2009 to 2010 was conducted in order to develop a model for identifying patients who will require increased doses of sedatives. Potential predictor variables including age, gender, endoscopy indication, high sedation requirements during previous endoscopies, difficulty of the procedure, bowel preparation quality, interventions, findings as well as current use of benzodiazepines, opioids and alcohol were analyzed. The outcome of study was the use of

high dose of sedation agents for the procedure. In particular, the high dose of sedation was defined as fentanyl greater than 50 mcg and midazolam greater than 3 mg.

RESULTS

Analysis of 5282 patients (mean age 57 ± 12 , 49% female) was performed. Most common indication for the procedure was screening colonoscopy (57%). Almost half of our patients received doses exceeding Fentanyl 50 mcg and Midazolam 3 mg. Logistic regression models identified the following variables associated with high sedation: Younger age (OR = 0.95 95%CI: 0.94-0.95; $P < 0.0001$); abdominal pain (OR = 1.45, 95%CI: 1.08-1.96); $P = 0.01$) and Inflammatory Bowel Disease (OR = 1.45, 95%CI: 1.04-2.03; $P = 0.02$) as indications for the procedure; difficult procedure as defined by gastroenterologist (OR = 1.73, 95%CI: 1.48-2.03; $P < 0.0001$); past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52; $P < 0.0001$) and previous colonoscopy (OR = 1.39, 95%CI: 1.21-1.60; $P = 0.0001$) and alcohol use (OR = 1.26, 95%CI: 1.03-1.54; $P = 0.02$). Age and gender adjusted analysis yielded inflammatory bowel disease as an indication (OR = 3.17, 95%CI: 1.58-6.37; $P = 0.002$); difficult procedure as defined by an endoscopist (OR = 5.13 95%CI: 2.97-8.85; $P = 0.0001$) and current use of opioids, benzodiazepines or antidepressants (OR = 2.88, 95%CI: 1.74-4.77; $P = 0.001$) having the highest predictive value of high sedation requirements. Our prediction model using the following pre-procedural variables including age, gender, indication for the procedure, medication/substance use, previous surgeries, previous high sedation requirements for colonoscopy yielded an area under the curve of 0.76 for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg.

CONCLUSION

Pre-procedural planning is the key in conducting successful, efficient colonoscopy. Logistic regression analysis of 5000 patients who underwent out-patient colonoscopy revealed the following factors associated with increased sedation requirement: Younger age, female gender, difficult endoscopy, specific indications as well as cardiopulmonary complications and current use of opioids/benzodiazepines. Age and gender adjusted analysis yielded similar results. These patients are more likely to need a longer recovery periods post-endoscopy, which could result in additional time and personnel requirements. The final predictive model has good predictive ability for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg and fair predictive ability for Fentanyl ≥ 50 mcg and Midazolam ≥ 2 mg. The external validity of this model is planned to be tested in another center.

Key words: Colonoscopy; Sedation; Sedation tolerance; Fentanyl; Midazolam; Predictive model

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Core tip: This manuscript explores patient specific

characteristics that are associated with increased sedation tolerance based on retrospective review of 5000 patients that underwent outpatient colonoscopies. Using a logistic regression analysis, we developed a predictive model that can identify patients requiring higher than usual sedation doses using pre-procedurally available patient parameters. The final prediction model that includes age, indication for the procedure, medication/substance use, previous surgeries yielded an area under the curve of 0.76 for Fentanyl ≥ 100 mcg and Midazolam ≥ 3 mg. This modelling could help optimize periprocedural planning and potentially identify patients who would benefit from alternative sedation methods, *e.g.*, propofol.

Shingina A, Ou G, Takach O, Svarta S, Kwok R, Tong J, Donaldson K, Lam E, Enns R. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. *World J Gastrointest Endosc* 2016; 8(20): 770-776 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i20/770.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i20.770>

INTRODUCTION

Lower gastrointestinal endoscopy remains a key modality for colorectal cancer evaluation and polyp detection. Patient satisfaction with colonoscopies remains an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite^[1]. Several prospective studies evaluated patient characteristics that influence endoscopy satisfaction and identified younger age, female gender, high levels of pre-procedure anxiety and current use of benzodiazepines/opioids as risk factors for decreased procedure tolerance^[2-5]. Currently a combination of benzodiazepines (*e.g.*, Midazolam) with opioids (*e.g.*, Fentanyl) is recommended for sedation during colonoscopic procedures. However, few predictive tools have been developed to accurately identify patients who will require higher than routine doses of procedural sedation.

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables as younger age, procedure indication, gender, trainee participation, psychiatric history and benzodiazepine and opioid use^[5]. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648. The development of an accurate predictive model could simplify procedure planning, eliminate unnecessary patient discomfort thereby improving patient satisfaction. It can also decrease peri-procedural time associated with administration of additional doses of sedatives and ultimately lead to a potentially increased diagnostic yield of the procedure.

In an attempt to address the paucity of data on factors associated with increased sedation rates in

colonoscopy we reviewed our experience in a large tertiary care hospital and developed a predictive tool that could be used for this purpose.

MATERIALS AND METHODS

Patient population and data gathering

A retrospective chart review was conducted on 5282 consecutive patients who underwent a non-urgent, outpatient colonoscopy within a two-year period between January 2009 and December 2010. Patients undergoing upper endoscopy on the same day were excluded. The final analysis included 5064 patients after patients with missing information and duplicate entries were excluded. Charts were reviewed and the following patient related variables were recorded: (1) age at the time of procedure; (2) gender; (3) indication for the procedure; (4) use of sedatives as well as doses; (5) past surgical history; (6) previous endoscopy; (7) high sedation requirements during previous endoscopy; (8) current use of benzodiazepines/opioids/antidepressants; and (9) current alcohol use. Furthermore, peri-procedural factors including: (1) quality of preparation; (2) difficulty of procedure as commented by the endoscopist; (3) finding on endoscopy; (4) interventions; and (5) cardiopulmonary complications.

Definitions

Increased sedation rates were defined as Fentanyl doses > 50 mcg and Midazolam doses > 3 mg a priori at the discretion of the endoscopists at our center. Increased sedation rates during previous endoscopic procedures followed the same definition. However, variable dose cut offs were subsequently tested in predictive models. Mild alcohol use was defined as less than 4 drinks/wk with moderate/severe defined as over 4 drinks/wk. Alcohol use was subsequently excluded from final analysis due to large proportion of missing data. Indication for the procedure was classified into one of five categories: (1) screening/surveillance; (2) abdominal pain; (3) inflammatory bowel disease (IBD); (4) lower gastrointestinal bleeding; (5) change in bowel movements.

Statistical analysis

Summary statistics were used to describe the characteristics of the study cohort. In particular, the data were summarized as mean, standard deviation, for continuous variables and count and percentage for categorical variables. We used a logistic regression model in an attempt to identify variables associated with higher than expected doses for midazolam and fentanyl. These variables were then included in the multivariate regression model.

In order to create a clinical prediction model of increased doses of sedation, multivariable logistic regression model with backward elimination based

Table 1 Study population characteristics

Variable	No. (%)
Age (mean ± standard deviation)	56.94 ± 13.06
Female gender	2306 (50.1%)
Indication of the procedure	
Screening/surveillance	2892 (57.15%)
Bleeding	1036 (20.4%)
Abdominal pain	240 (4.72%)
Change in bowel movements	690 (13.64%)
Inflammatory bowel disease	210 (3.99%)
Previous history of surgery	
No	2343 (50.7%)
Yes	2363 (49.26%)
Previous history of colonoscopy and of increased dose of sedation for colonoscopy	
Colonoscopy with high dose (Fent > 50 mcg, Midazolam > 3 mg)	3300 (64.1%)
Colonoscopy with standard dose	470 (9.1%)
Colonoscopy with unknown sedation dose	305 (5.9%)
No previous colonoscopy	1076 (20.9%)
Current use of opioids	243 (4.8%)
Current use benzodiazepines	254 (5%)
Current use antidepressants	589 (11.6%)
Current use of opioids or benzodiazepines or antidepressants	826 (16.96%)
Difficult procedure	1038 (19%)
Cardiopulmonary complications	23 (0.4%)
Findings	
Any	4139 (78%)
Polyps	3439 (83%)
Haemorrhoids	1970 (48%)
Diverticuli	1050 (35%)
Colitis	72 (1.7%)
Stricture	71 (1.7%)
Intervention	
Any	3231 (61%)
Biopsy	2139 (66%)
Polypectomy	1621 (50%)
Current use alcohol	1930 (46.9%)
Fentanyl dose > 50 mcg	2244 (46%)
Midazolam dose > 3 mg	3000 (62%)
Fentanyl dose > 50 mcg and midazolam > 3 mg	1959 (40%)

on Akaike Information Criterion was applied^[7]. The performance of the final model was evaluated from two aspects, discrimination (the ability to discriminate patients who need high doses and those that do not) and calibration (the agreement between observed outcomes and model predictions). The discrimination of the model was measured with the use of the area under ROC curves. Discrimination is assumed to be useful if $AUC \geq 0.75$ ^[6]. Furthermore, we applied bootstrapping technique to account for model over-fitting as internal model validation. Three hundred bootstrapping samples were created. A biased corrected AUC and calibration plot were generated. All statistical analysis was performed using SAS software. The statistical methods of this study were reviewed by Oliver Takach, Dr. Eric Lam, Terry Lee and Hong Qian.

Table 2 Multivariate logistic regression analysis for Fentanyl dose > 50 mcg

Variable for fentanyl > 50 mcg	Coefficient	P value	OR (95%CI)
Age	-0.04	0.0001	0.957 (0.952-0.963)
Indication for endoscopy (reference - screening)			
Bleeding	-0.04	0.62	0.96 (0.82-1.12)
Abdominal pain	0.29	0.06	1.34 (0.99-1.81)
Change in BM	0.07	0.44	1.08 (0.88-1.31)
IBD	0.46	0.009	1.59 (1.22-2.49)
Intraprocedural characteristics			
Difficult procedure	0.45	0.0001	1.57 (1.34-1.81)
Intervention	0.15	0.013	1.17 (1.033-1.32)
Bad preparation	0.16	0.14	1.17 (0.94-1.45)
Past history			
Abdominal surgery	0.33	0.0001	1.40 (1.23-1.59)
Colonoscopy	0.26	0.0002	1.30 (1.13-1.49)
Current medications/substance use			
Opioids	0.34	0.028	1.40 (1.03-1.91)
Benzodiazepines	0.37	0.017	1.45 (1.06-1.98)
Antidepressants	0.26	0.009	1.30 (1.06-1.60)
Alcohol	0.23	0.022	1.26 (1.03-1.54)
(any <i>vs</i> none)			

IBD: Inflammatory bowel disease; BM: Bowel movements.

RESULTS

Characteristics of study population

The study population consisted of 50.1% females, mean age of 56 years (Table 1). The most common indication for colonoscopy was malignancy screening/surveillance that accounted for 57% of procedures. Approximately half of the population had some history of abdominal surgery (49%) and colonoscopy (79%). The use of opioids, benzodiazepines and antidepressants was identified in 4.8%, 5% and 11.6% of patients respectively or 17% of all patients on any of the three drugs. There was a significant proportion of alcohol use data missing (30%); of patients on whom the data was available 46% used alcohol on a regular basis.

The procedure was identified as difficult in 19% by a gastroenterologist. The most common cause for difficult procedure was identified as "tortuous colon" accounting for almost 50%, followed by looping of the colonoscope in 20% of patients. Poor preparation and patient discomfort was identified as a reason in 2% and 3% respectively. Cardiopulmonary complications were recorded in 0.4% of procedures. Presences of any findings were seen in 78% of procedures with polyps being the most common one (83%). Interventions were carried out in 61% of all colonoscopies, most common of those being a biopsy (66%).

Logistic regression analyses to identify variables predicting high sedation doses

Univariate logistic regression analysis revealed that younger age, indication for colonoscopy, intraprocedural characteristics such as difficult procedure, interventional procedure, poor preparation, past history of abdominal

Table 3 Multivariate logistic regression analysis for midazolam dose > 3 mg

Variable for midazolam > 3 mg	Coefficient	P value	OR (95%CI)
Age	-0.05	0.0001	0.94 (0.939-0.95)
Female gender	-0.06	0.0004	0.78 (0.68-0.89)
Indication for endoscopy (reference - screening)			
Bleeding	-0.41	0.0001	0.65 (0.56-0.77)
Abdominal pain	0.38	0.032	1.46 (1.03-2.08)
Change in BM	0.02	0.849	1.02 (0.82-1.25)
IBD	0.19	0.346	1.21 (0.81-1.80)
Intraprocedural characteristics			
Difficult procedure	0.50	0.0001	1.64 (1.38-1.96)
Past history			
Abdominal surgery	0.31	0.0001	1.37 (1.20-1.57)
Medication/substance use			
Opioids	0.38	0.025	1.47 (1.04-2.07)
Antidepressants	0.33	0.018	1.39 (1.11-1.73)

IBD: Inflammatory bowel disease; BM: Bowel movements.

surgery as well as substance use were independently predictive of increased Fentanyl doses defined as more than 50 mcg (data not shown). Including these variables in the multivariate regression model showed that younger age (OR = 0.95, 95%CI: 0.95-0.96), presence of IBD (OR = 1.59, 95%CI: 1.22-2.49), difficult procedure (OR = 1.57, 95%CI: 1.34-1.81), presence of intervention (OR = 1.17, 95%CI: 1.03-1.32), past history of surgery (OR = 1.4, 95%CI: 1.23-1.59) and colonoscopy (OR = 1.3, 95%CI: 1.13-1.49) were predictors of Fentanyl doses over 50 mcg (Table 2).

Similar multivariate analysis of Midazolam dosages over 3 mg revealed female gender (OR = 0.78, 95%CI: 0.68-0.89) in addition to younger age (OR = 0.94, 95%CI: 0.93-0.95), presence of bleeding (OR = 0.65, 95%CI: 0.56-0.77) and abdominal pain (OR = 1.46, 95%CI: 1.03-2.08) as indications for the procedure, difficulty of the procedure (OR = 1.64, 95%CI: 1.38-1.96), history of abdominal surgery (OR = 1.37, 95%CI: 1.20-1.57) as well as opioid (OR = 1.47, 95%CI: 1.04-2.07) and antidepressant use (OR = 1.39, 95%CI: 1.11-1.73) (Table 3).

Multivariate regression analysis of patients requiring both Fentanyl dose of over 50 mcg and midazolam dose over 3 mg revealed the following significant variables: Younger age (OR = 0.95, 95%CI: 0.94-0.95), abdominal pain (OR = 1.45, 95%CI: 1.08-1.96) and IBD (OR = 1.45, 95%CI: 1.04-2.03) as indications for the procedure, difficult procedure (OR = 1.73, 95%CI: 1.48-2.03), past history of abdominal surgery (OR = 1.33, 95%CI: 1.17-1.52) and colonoscopy (OR = 1.39, 95%CI: 1.21-1.60) as well as alcohol use (OR = 1.26, 95%CI: 1.03-1.53) (Table 4).

Age and gender adjusted analysis

Since previously published literature identified younger age and female gender as predictors of high sedation requirements, we also carried out age and gender

Table 4 Multivariate regression analysis of both Fentanyl > 50 mcg and Midazolam > 3 mg

Variable for Fentanyl > 50 mcg and midazolam > 3 mg	Coefficient	P value	OR (95%CI)
Age	-0.04	< 0.0001	0.95 (0.94-0.95)
Indication for endoscopy (reference - screening)			
Bleeding	-0.11	0.18	0.89 (0.76-1.05)
Abdominal pain	0.37	0.01	1.45 (1.08-1.96)
Change in BM	0.13	0.18	1.14 (0.93-1.40)
IBD	0.37	0.02	1.45 (1.04-2.032)
Intraprocedural characteristics			
Difficult procedure	0.55	< 0.0001	1.73 (1.48-2.03)
Interventions	0.1	0.12	1.10 (0.97-1.25)
Past history			
Abdominal surgery	0.30	< 0.0001	1.33 (1.17-1.52)
Colonoscopy	0.33	0.0001	1.39 (1.21-1.60)
Medication/substance use			
Opioids	0.41	0.46	0.49 (0.07-3.36)
Benzodiazepines	0.36	0.36	3.76 (0.21-64)
Antidepressants	0.22	0.6	0.48 (0.03-7.76)
Alcohol	0.23	0.02	1.26 (1.03-1.54)

BM: Bowel movements; IBD: Inflammatory bowel disease.

adjusted analyses (Supplemental Table 1). Significance of only one variable changed: Abdominal pain as an indicator for the procedure was no longer statistically impacting the higher dose of sedation medications ($P = 0.03$ in unadjusted vs $P = 0.06$ in age/gender adjusted analysis).

Development of predictive model

To predict patients who will require higher than routine doses of procedural sedation before the procedure, a prediction model was created using patient characteristics recorded at admission. Age, gender, previous history of surgery, previous history of colonoscopy with high dose, indication of the procedure and current use of opioids, benzodiazepines, antidepressants or alcohol were included in the final model for predicting the use of fentanyl > 50 mcg plus midazolam > 3 mg (Table 5).

In our model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies with high sedation, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The bootstrapping bias corrected ROC AUC of the final prediction model was 0.66 for Midazolam > 3 mg and Fentanyl > 50 mcg doses indicating moderate discriminative ability (supplemental material).

We analysed the predictive ability of our model in variable higher Fentanyl and Midazolam doses (Table 6). The model using Fentanyl > 100 mcg and Midazolam > 3 and 4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Table 5 Multivariable prediction model for high Fentanyl and Midazolam doses

Pre-procedural variables	Measurement units	Odds ratio, 95%CI; P value
Age	10-yr	0.62, 0.52-0.73; $P < 0.0001$
Gender	Female vs male	2.31, 1.32-4.05; $P = 0.01$
Previous colonoscopy with high sedation	Yes vs no	1.98, 1.15-3.42; $P = 0.02$
Previous surgery	Yes vs no	1.33, 0.78-2.25; $P = 0.25$
Current use of opioids, benzodiazepines or antidepressants	Yes vs no	2.50, 1.47-4.27; $P = 0.004$
Indications (reference - screening)	Bleeding	1.90, 1.03-3.51; $P = 0.04$
	Abdominal pain	3.07, 1.29-7.31; $P = 0.01$
	Change in BM	1.45, 0.71-2.97; $P = 0.30$
	IBD	3.01, 1.43-6.35; $P = 0.01$

BM: Bowel movements; IBD: Inflammatory bowel disease.

DISCUSSION

Pre-procedural planning is key for successful and efficient colonoscopy. Identifying patients requiring higher sedation rates could optimize sedation methods and use of scheduling with improved efficiency in addition to better tolerated procedures.

Our analysis of over 5000 patients yielded several prediction variables of high sedation rates. These included: Younger age, indication for the procedure, difficulty of the procedure, previous history of high endoscopy sedation requirements and substance use. A predictive model including patients' age, indication for procedure, medication/substance use, previous surgeries as well as previously high sedation requirements yielded a good predictive model. These factors can help physicians in planning endoscopy slates and ensure appropriate time can be booked for procedure completion.

To our knowledge, this is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies. Another predictive model was recently described by Braunstein *et al*^[5] after reviewing data on 13711 EGDs and 21763 colonoscopies using a retrospective database in the United States. In contrast to our study, the stratifying clinical outcomes prior to endoscopy (SCOPE) scoring system included inpatient colonoscopies as well as used a composite endpoint of sedation doses in top quintile stratified per endoscopist plus endoscopist report of patient discomfort or agitation during the procedure. The SCOPE model did not evaluate previous surgical or endoscopic history of the patients, however it did include the use of tobacco and lower BMI. Despite these differences, the final model for colonoscopy prediction tool was similar to ours perhaps validating our findings despite a smaller sample size. The predictive value of the SCOPE class model remained only moderate with areas under the ROC curves of 0.648 and comparable to ours at 0.7. It is possible that the moderate predictive

Table 6 Performance of prediction model using variable sedation doses cut-offs

Fentanyl (mcg)	Midazolam (mg)	AUC	Prevalence rate
> 50	> 3	0.67	43%
> 50	> 4	0.70	22%
> 75	> 3	0.68	23%
> 75	> 4	0.70	18%
> 100	> 3	0.76	2%
> 100	> 4	0.77	2%

AUC: Area under the curve.

ability of both models is attributed to variables that could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (*e.g.*, propofol) and may serve as a starting point in pre-endoscopic assessment.

This study has several limitations. First, our experience is limited to one tertiary care center with eight endoscopists. As such, it may have limited generalizability to other centers and perhaps could reflect the specific sedation preferences of individual endoscopists. Second, a large proportion of substance and alcohol use data was missing which could otherwise improve the discriminatory ability of our predictive model. Third, this was a retrospective review study and the model needs to be prospectively evaluated. Finally, propofol was not assessed in this study as it is not commonly used in a Canadian population and as such this study may not be applicable to this patient population.

Further prospective studies are needed to test the model in order to increase its generalizability and also potentially incorporating subjective variables such as patient anxiety and endoscopist subjective judgement.

ACKNOWLEDGMENTS

We would like to thank Terry Lee and Hong Qian for providing statistical support for the analysis; Joseph Frenette for assistance with data collection/sorting; the Department of Gastroenterology of the Saint Paul Hospital for the support with this project.

COMMENTS

Background

Patient satisfactions with colonoscopies remain an important area for quality improvement and have been linked to the ability to achieve adequate sedation in the endoscopy suite. Predicting which patients may require high doses of opioid/benzodiazepine combination may help with peri-procedural planning (*e.g.*, accounting for longer recovery times, using alternative sedation methods such as propofol) and improve overall patient experience.

Research frontiers

Recently, one model using a retrospective database was used to evaluate patient pain thresholds included such variables younger age, procedure indication,

gender, trainee participation, psychiatric history and benzodiazepine and opioid use. However, this model reached only moderate discriminative ability with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.648.

Innovations and breakthroughs

This is the first and the largest study using Canadian data that describes sedation tolerance in outpatient colonoscopies to our knowledge. In this model the probability of high dose correlated negatively with younger age, with proportional decrease for every 10 years of life, female gender, previous colonoscopies, and history of surgical procedures, composite of current use of opioids/benzodiazepines/antidepressants as well indications for the procedure. The model for predicting patients requiring Fentanyl > 100 mcg and Midazolam > 3-4 mg reached the acceptable level of discrimination ability of 0.7 and remained under 0.8 indicating its moderate discrimination ability.

Applications

The analysis of over 5000 patients yielded a moderately predictive model for identifying patients requiring high opioid/benzodiazepine doses. This is in concordance with previously reported models in SCOPE study. It is possible that the moderate predictive ability of both models is attributed to variables that could not be extracted from retrospective data, such as the patient's pre-procedural anxiety as well as the subjective discretion of the endoscopist. Nevertheless, these models may help in pre-identifying patients that may benefit from deeper sedation (*e.g.*, propofol) and may serve as a starting point in pre-endoscopic assessment.

Terminology

To assess the ability of the prediction model to discriminate patients who need high doses with those don't, the concordance statistics (C-index) was calculated. The C-index is equivalent to the area under ROC curve and ranges from 0 to 1. A value of 0.5 is considered as no discrimination ability. As a general rule, a value between 0.7 and 0.8 is considered the threshold for acceptable discriminatory performance and a value of > 0.8 is considered to be the threshold for excellent discriminatory performance.

Peer-review

This paper presents the results of retrospective analysis of sedation dose requirement of benzodiazepine with opiates used for colonoscopy. The basic objective of the study was to provide the data as to the optimization of sedation conditions for patients undergoing colonoscopy. The data obtained with 5000 patients support the notion that the predictive model can help to identify patients requiring higher than usual sedation doses. Statistical analyses were conducted in detail and authors have led a conclusion based on the findings. That was helpful for us to identify patients that may require higher sedation doses for successful and efficient colonoscopy.

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P- Reviewer: Muguruma N, Slomiany B, Yu B
S- Editor: Qiu S **L- Editor:** A **E- Editor:** Wu HL





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