Tolerance and Safety to Colonoscopy with Conscious Sedation in Malaysian Adults

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SUMMARY

Tolerance to colonoscopy varies between populations and data from the South East Asian region is lacking. We aimed to determine tolerance and safety with to colonoscopy; conscious sedation and identify risk factors for complications in Malaysian adults. Consecutive outpatients undergoing colonoscopy were enrolled prospectively. A combination of pethidine and midazolam were used and tolerance to colonoscopy assessed three hours post-procedure using a validated scale. All patients were monitored for cardio-respiratory depression and risk factors for complications were identified. Two hundred and eight patients (mean age 57.2 ± 14.8 years, 48% female) were enrolled. The population ethnicity consisted of 45 (21.63%) Malays, 101 (48.56%) Chinese and 56 (26.92%) Indians. Conscious sedation was achieved with 5.0 ± 1.1mg of midazolam and 43.3 ± 14.0 mg of pethidine. Thirty (14.4%) patients tolerated the procedure poorly and independent predictors included female gender (OR 2.93, 95% CI=1.22 to 7.01) and a prolonged duration of procedure (OR 2.85, 95% CI=1.08 to 7.48). Hypotension occurred in 13 (6.25%) patients, with age > 65 years as the only risk factor (OR 13.17, 95% CI=1.28 to 137.92). A prolonged duration was the main cause of hypoxia (OR 5.49, 95% CI=1.54 to 19.49), which occurred in 6 (2.88%) patients. No major complications occurred during the study period. The current practice of conscious sedation is safe and tolerated well by most adults in our population. However, poor tolerance in a notable minority may have significant clinical implications.

INTRODUCTION

The incidence of colorectal cancer is increasing in Asia [1-3] and the situation in South East Asia, especially in a rapidly developing country like Malaysia, is no different[4-5]. Colonoscopy remains the most accurate and specific tool in diagnosing this disease[6]. Successful colonoscopy depends on a complete examination of the colon with clear views of the lumen, which can only be obtained with adequate bowel preparation (cleansing) and a patient who tolerates the procedure without much difficulty. However, colonoscopy is invasive and many patients find the procedure uncomfortable.

Current clinical practice in most parts of the world involves the use of sedative and/or analgesic drugs to allow for adequate patient tolerance during the procedure[7]. However, geographical and cultural variations with regards to the requirement of sedation for colonoscopy is well recognised. For example, in the United Kingdom (U.K.) and the United States (U.S.), sedation in the form of midazolam and pethidine are routinely administered for patients[8]. In France, most colonoscopy is performed under general anesthesia [9]. In contrast, in countries like Norway and Japan, sedation is rarely required and colonoscopy is usually performed in alert patients who appear to tolerate the procedure without much discomfort[10]. There is little, if any, data from Southern Asian populations, but a varied tolerance is expected, especially with the observed lower pain threshold in South Asians[11].

In Malaysia, we have adopted a U.K/ U.S. – style of sedation practice with a combination of midazolam and pethidine for colonoscopy. However, little is known about the degree of tolerance to this regime of conscious sedation and the clinical safety to the combination of these drugs in Malaysians. The use of conscious sedation carries a small but significant risk of cardio-respiratory depression[12], longer recovery time and more nursing support[13]. Previous data from this institution has shown that the population undergoing colonoscopy for various indications were mainly in the older age group with more co-morbidity[14]. Data on safety using our current regimen of conscious sedation is therefore important to minimize complications in this elderly population.

In this tertiary institution, we perform close to 2000 colonoscopies annually, serving a population of 700,000. The aims of this study were:

1. To determine the local population tolerance to colonoscopy and identify risk factors for poor tolerance
2. To examine the safety of the current practice of conscious sedation and identify risk factors for cardio-respiratory depression during colonoscopy.

MATERIALS AND METHODS

Consecutive adult outpatients undergoing colonoscopy at this institution were prospectively enrolled into the study. This combined endoscopy unit has an open access referral system for our local primary care physicians and all hospital clinicians (usually general surgeons or Gastroenterologists). Approval was gained by the local institutional ethics committee (in accordance with G.C.P/I.C.H. guidelines) and patients provided written informed consent before participation in the study. Patients with the following criteria were excluded: inability to speak or write, inpatients, patients with previous colonic surgery, major psychiatric disease

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(dementia, schizophrenia, and depression), known hypersensitivity to midazolam or pethidine, history of drug addiction, chronic benzodiazepine use, and absence of contact telephone. Regular alcohol consumers were advised to abstain from alcohol for a minimum of two days prior to examination.

Prior to colonoscopy, all study patients were asked to complete a self-administered questionnaire collecting basic demographic data and the 7-question anxiety subscale of the Hospital Anxiety and Depression (HAD) scale[15]. For the purpose of analysis we divided the indications for colonoscopy into irritable bowel syndrome (IBS) and non-IBS. IBS was defined as per the Rome II criteria[16] which mainly constituted chronic abdominal pain and chronic diarrhea in our patient population. All patients were administered a combination of intravenous midazolam and pethidine. The starting doses of midazolam and pethidine were 2.5mg and 25mg respectively for patients >60 years or low BMIs; and 5mg and 50mg respectively for patients <59 years. Both drugs were increased if necessary during the examination if the patient expressed pain or discomfort verbally to the individual endoscopist or nurse assistant. Titration of either midazolam and/or pethidine to achieve optimal conscious sedation was performed according to individual endoscopists' preference. Continuous monitoring of oxygen saturation, blood pressure, and pulse rate was undertaken. The duration of the procedure was recorded from the time of insertion through the anus (including diagnostic and/or various therapeutic procedure if applicable) until the withdrawal of tip of the colonoscope from the anus.

All colonoscopies were performed using standard video-colonoscopes (Olympus CF 130L, Olympus Optical, Tokyo, Japan). To enhance the clinical relevance of this study to most public institutions, we decided to examine procedures performed by various grades of physicians. Their level of experience was divided as follows: <1 year (trainees), 1-5 years (middle-grades) and >5 years (senior endoscopists). Colonoscopy performed by trainees were usually initiated by them, but supervisors would take over when trainees were unable to negotiate beyond bends/ loops despite persistent attempts, or when trainees themselves decided that they were unable to proceed further. Details of the procedure including indication for colonoscopy, level of difficulty as assessed by the operator, caecal intubation rate, adequacy of bowel preparation (poor, satisfactory, good) and any additional procedures performed were documented. The starting and final cummulative dose of midazolam and pethidine were recorded, together with any complications encountered. Hypotension was defined as mean arterial pressure (MAP) of less than 60 mmHg. Hypoxia was defined as decrease in oxygen saturation to below 90% during three or more consecutive measurements, with at least 12-second time interval between measurements[10].

A member of staff who was blinded to the amount of sedation administered assessed all patients for pain and tolerability using a 10-cm visual analog score of 1-100 (VAS)[17], one to three hours after colonoscopy. To avoid recall bias due to retrograde amnesia from midazolam, a brief memory test consisting of events just prior to the procedure (corroborated by individuals escorting the patient home) was done prior to confirming the VAS. An additional 5 – level Likert scale for patient discomfort (level 1=nil, level 2=minimal, level 3=mild, level 4=moderate, level 5=severe)[18] was used to counter-check the VAS. In an earlier pilot study of twenty patients (unpublished), we defined poor tolerance as a VAS of > 50mm, which correlated well with level 4 and 5 discomfort on the Likert scale. The patients were also asked for willingness for repeat procedure in the same manner if needed in the future. Twenty-four to 72 hours after the procedure, the patient received a phone call to assess for abdominal pain, any complications related to the procedure or conscious sedation.

Statistics

Data analysis was performed using a standard statistical software programme (SPSS Inc., version 11.0, Chicago, USA). Categorical data were assessed with the chi-square test. All continuous variables were expressed as means and were analysed using Student's t-test or Fisher's exact method where appropriate. Individual factors for poor tolerance and cardio-respiratory complications were analysed using univariate analysis. Independent risk factors were then identified using multiple logistic regression analysis. Results with p values of < 0.05 were considered statistically significant.

RESULTS

A total of 208 patients were enrolled into the study between September 2004 and February 2005. The mean age of patients was 57.2 ± 14.8 years (range 16 - 85) and the sex ratio was 1.08 male: 1 female. Details of the demographic data are shown in Table I. Anxiety, as assessed by the HAD score was present in 25 (12.02%) patients undergoing colonoscopy. To the best of our knowledge, no patients were taking benzodiazepines, anxiolytics or antidepressants during the period of study. The majority of the examinations were index colonoscopies, while the other indications included repeat examinations for polyp surveillance (n=28), cancer surveillance (n=23), inflammatory bowel assessment (n=6) and colonic ulcer (non-IBD) reassessment (n=9). It is likely that the latter group may have had lower HAD scores, but tolerance was unlikely to be affected.

Bowel preparation was found to be good or satisfactory in 170 (81.7%) cases and complete examinations (i.e. caecal intubation) was achieved in 183 (87.98%) cases. Supervised trainees (<1 year experience) performed 145 cases (69.71%), with supervision from senior endoscopists. This was not surprising due to the large number of trainees in this tertiary institution. The mean duration of colonoscopy was 27.8 ± 11. 5 minutes. However, we noted that there were significant differences in median total colonoscopy times between the grades of doctors: 16.5 minutes for endoscopists >5 year experience, compared to 25 minutes for endoscopists with <5 years experience (p=0.02).

Mean doses of midazolam (trainee 4.9 ± 0.9mg, middle-grade 5.1 ± 1.4mg, senior 4.6 ± 0.9mg) and Pethidine (trainee 41.5 ± 14mg, middle-grade 48.5 ± 14mg, senior 42.9 ± 11mg) used to achieve conscious sedation were not significantly different between the grades of endoscopists. 164 (78.8%) examinations were purely diagnostic, whilst 26 (12.5%) cases required polypectomy and 18 (8.7%) patients needed

chromoendoscopy/ multiple biopsies. Although non-diagnostic colonoscopy clearly took longer (34.9 ± 13 mins vs 25.9 ± 10 mins) than purely diagnostic examinations, no differences in midazolam doses (4.8 ± 0.8mg vs 5.0 ± 1mg) nor pethidine use (44.9 ± 13mg vs 43.0 ± 14mg) were noted between the two.

Tolerance to colonoscopy

Thirty patients (14.42%) were found to have poor tolerance to colonoscopy. No differences in sedation doses were noted in patients who had poor or good tolerance to colonoscopy. Mean doses of midazolam administered between patients who had poor tolerance and the others in the group was not different (5.0 ± 1.0 mg vs 4.9 ± 1.2 mg, p=0.11). Similarly, mean doses for pethidine did not vary significantly either (45.83 ± 17.47mg poor tolerance vs 42.8 ± 13.3 mg others, p=0.55). Univariate analaysis revealed that female gender, IBS as an indication, difficult colonoscopy and duration of procedure of more than 30 minutes were significant associations of poor tolerance (Table II). However, when logistic regression analysis was performed on these factors, only female gender (odds ratio 2.93, 95% CI=1.22 to 7.01) and duration of procedure of more than 30 minutes (odds ratio 2.85, 95% CI=1.08 to 7.48) were revealed as independent predictors of poor tolerance.

When patients were enquired about willingness to repeat colonoscopy using the same sedation regime that they had, 15/30 patients (50%) who had poor tolerance declined to have this done again as compared to only 4 (2.25%) patients who tolerated colonoscopy well (p< 0.001).

Cardiorespiratory complications

Hypotension occurred in six patients (2.88%) undergoing colonoscopy. All were aged 65 years and above with the mean age of 67.8 years. The mean doses of midazolam and pethidine used were not significantly different between the patients who did and did not develop hypotension (Table IIIa). Various potential risk factors for hypotension were analysed (Table IIIa) and age > 65 years was found to be significant. Multiple logistic regression analysis subsequently confirmed that age > 65 years was an independent risk factor for hypotension (odds ratio 13.17, 95% CI=1.28 to 137.92) in our adult population undergoing colonoscopy. Hypoxia occurred in 13 (6.25%) of the study patients. Univariate analysis revealed that duration >30 minutes a BMI >25 and female gender were associated with hypoxia (Table IIIb). However, duration (of colonoscopy) >30 minutes was again found to be the only independent predictive factor for hypoxia at multiple logistic regression analysis (odds ratio 5.49, 95% CI=1.54 to 19.49).

In all patients who developed cardio-respiratory depression, no serious complications occurred. Hypoxia was reversed mostly with oxygen and only six patients required reversal agents. Hypotension was not prolonged in all patients and resolved spontaneously upon patient recovery. No patients required hospitalization and a 72 hour post-procedure telephone check confirmed no delayed complications either.

DISCUSSION

There is a lack of data from the Asian continent on patients' tolerance to colonoscopy. It is well recognised that cultural differences exist with regards to tolerance and requirements for sedation/ analgesia [7]. Recent observations in pain perception have revealed that clear differences exist between Asian and Caucasian adults [11], and hence we cannot assume that South/ South East Asians tolerate colonoscopy similarly to their European/American counterparts. A major limitation from this study was the fact that most of the colonoscopies were performed by trainees, with senior supervision. Hence, our data may not reflect the experiences of individual senior/ experienced endoscopists of this country. However, the ratio of endoscopy staff quoted in this study is representative of most public tertiary/training institutions in this country. Furthermore, colonoscopic performance, i.e. median time for total colonoscopy and caecal intubation rates, of senior and trainee endoscopists from our unit are comparable with other institutions from the West [30-33].

We have demonstrated that 14.4% of adult patients have poor tolerance to outpatient colonoscopy in routine clinical practice. No differences in sedative or analgesic doses existed between patients who reported poor tolerance and the others. Amongst the various factors that we examined, female gender

Table I: Demographic data and indications for colonoscopy (n=208)

Age (years), mean ± SD	57.2 ± 14.8
Sex, female (%)	100 (48.0)
Race, Malay (%)	45 (21.6)
Chinese (%)	101 (48.5)
Indian (%)	56 (26.9)
Others (%)	6 (2.8)
BMI, mean ± SD	23.3± 4.0
Education level, below tertiary (%)	150 (72.1)
Previous non-colonic surgery (%)	84 (40.3)
Index colonoscopy (%)	142 (68.3)
Altered bowel habit	48 (23.1)
chronic abdominal pain	43 (20.7)
hematochezia/ anemia	36 (17.3)
polyp surveillance	28 (13.4)
genetic cancer risk	23 (11.0)
chronic diarrhea	15 (7.2)
inflammatory bowel diseases assessment	6 (2.8)
others	9 (4.2)

Table II: Factors predicting poor tolerance: Univariate analysis

Variables		Tolerance, n (%)		P value	Odds ratio	95% CI
		Good	Poor			
Age, years	≤ 65	118 (66.3)	18 (60)	0.503	1.311	0.593, 2.900
	> 65	60 (33.7)	12 (40)			
BMI	< 25	118 (66.3)	18 (60)	0.503	1.311	0.593, 2.900
	≥ 25	60 (33.7)	12 (40)			
Gender	Female	79 (44.4)	21 (70)	0.009	2.924	1.269, 6.739
	Male	99 (55.6)	9 (30)			
Race	Malay	36	9	0.17	- 1.36	-0.51, 0.90
	Indian	49	7			
	Chinese	87	14			
First-timer	Yes	118 (66.3)	24 (80)	0.136	2.034	0.789, 5.244
	No	80 (33.7)	6 (20)			
Education level	≥ tertiary	51 (28.7)	7 (23.3)	0.548	0.758	0.306, 1.876
	< tertiary	127 (71.3)	23 (76.7)			
Previous abdominal/pelvic surgery						
	Yes	72 (41.5)	12 (40)	0.963	0.981	0.446, 2.161
	No	106 (59.5)	18 (60)			
Anxious	Yes	19 (11.7)	6 (20)	0.146	2.092	0.760, 5.763
	No	159 (89.3)	24 (80)			
Indication	IBS	45 (26.3)	13 (44.3)	0.041	0.442	0.199, 0.982
	Non-IBS	133 (74.7)	17 (56.7)			
Bowel prep.	good	83 (46.6)	9 (30)	0.090	2.039	0.885, 4.696
	satisfactory/poor	95 (54.4)	21 (70)			
Ease of colonoscopy	easy	105 (58.9)	11 (36.7)	0.023	2.484	1.116, 5.531
	difficult	73 (42.1)	19 (63.3)			
Procedure	diagnostic	142 (79.7)	22 (73.3)	0.424	1.434	0.590, 3.486
	therapeutic	36 (21.3)	8 (26.7)			
Endoscopists'experience:	≤ 1 year	123	22	0.641	0.813	0.341, 1.940
	1 – 5 years	44	5			
	> 5 years	11	3			
Complete colonoscopy	Yes	158 (88.8)	25 (83.3)	0.397	0.633	0.218, 1.840
	No	20 (11.2)	5 (16.7)			
Duration	≤ 30 min	126 (70.8)	14 (46.7)	0.009	2.769	1.261, 6.081
	> 30 min	52 (29.2)	16 (53.3)			

Table IIIa: Risk Factors for Hypotension (Univariate)

	Hypotension		p	Odds Ratio	95%CI
	Yes (n=6)	No (n=202)			
Midazolam (mg) mean± SD	4.5 ± 1.0	5.0 ± 1.0	0.37	0.65	0.25, 1.67
Pethidine (mg) mean± SD	45.8 ± 10.2	43.19 ± 14.1	0.12	1.05	0.99, 1.11
Duration > 30 mins	1 (16.7%)	67 (33.2%)	0.39	0.40	0.04, 3.52
Age > 65 years	5 (83.3%)	67 (33.2%)	0.01	10.08	1.15, 87.96
BMI > 25	1 (16.7%)	71 (35.1%)	0.35	0.37	0.04, 3.22
% Females	3 (50%)	97 (48%)	0.92	1.08	0.21, 5.49
Endoscopist's experience:					
< 1 year	5 (83.3%)	140 (69.3%)	0.60		
1-5 years	1 (16.7%)	48 (23.8%)		0.53	0.54, 5.31
> 5 years	0	14 (6.9%)			

Table IIIb: Risk factors for Hypoxia (univariate)

	Hypotension		p	Odds Ratio	95% CI
	Yes (n=13)	No (n=195)			
Midazolam (mg) mean± SD	5.0 ± 1.02 5.0 ± 1.07	5.0 ± 1.07	0.69	0.89	0.51, 1.56
Pethidine (mg) mean± SD	46.15 ± 13.87	43.08 ± 14.02	0.73	1.00	0.96, 1.06
Duration > 30 mins	9 (69.2%)	59 (30.3%)	0.004	5.19	1.54, 17.51
Age > 65 years	3 (23.1%)	69 (35.4%)	0.36	0.55	0.15, 2.06
BMI > 25	6 (46.2%)	66 (33.8 %)	0.36	1.66	0.54, 5.19
% Females	8 (61.5%)	92 (47.2%)	0.32	1.80	0.56, 5.67
Endoscopist's experience:					
< 1 year	11 (84.6%)	134 (68.7%)	0.32		
1-5 years	2 (15.4%)	47 (24.1%)		0.43	0.08, 2.25
> 5 years	0	14 (7.2%)			

and prolonged duration of the procedure (>30 minutes) were the main predictors of poor tolerance. Female gender as a predictor of poor tolerance to colonoscopy has been demonstrated previously[10]. Possible explanations include longer colons in female[19], lesser intra-abdominal fat as compared with men (differences in fat distribution according to sex), and larger pelvic cavity which allow more loops to form[20]. The relatively larger amount of intra-abdominal fat found in men will support the advancement of a colonoscope and allow easier passage through the colonic lumen. Women, on the other hand, are more likely to have gluteal or femoral fat. A further explanation for the gender difference in tolerance could include the fact that men tend to have more musculature that provides resistance to the colonoscope and thus prevents looping.

A prolonged duration of colonoscopy may have several reasons. Commonly recognised causes for prolonged colonoscopy include operator inexperience, difficult colonic anatomy (looping, diverticula, etc), performance of therapeutic interventions and poor bowel preparation. Although no obvious differences in bowel preparation were encountered, difficulty encountered by the endoscopist was found to be a significant association with poor tolerance at univariate analysis. Likewise, operator experience did not appear to influence patient tolerance to colonoscopy, but this is most probably due to the greater number of junior endoscopists in our study, resulting in a statistical Type 2 error. We noted that junior endoscopists took a significantly longer time to complete colonoscopic examination compared to senior endoscopists. Therefore, it is possible that a prolonged procedure time may have been a surrogate marker for operator inexperience and difficult colonoscopy. However, other studies have also demonstrated a similar lack of association between operator experience and patient tolerance[21].

In our population, pre-procedure anxiety was not predictive of poor tolerance, but IBS-type symptoms were strongly associated with it. Our findings have some similarity with previous published data, where patients with chronic constipation, laxative abuse or chronic abdominal pain as an indication were more likely to experience more pain during colonoscopy [20]. It is possible that the smaller numbers of patients with IBS-type symptoms in our cohort may have resulted in this factor's exclusion as a significant predictor in the multi-variate analysis. The multi-racial nature of our patient population enabled us to conclude that ethnicity had no bearing on patient tolerance to colonoscopy. This was slightly surprising due to the cultural differences in sedation practices for colonoscopy mentioned beforehand. However, to our knowledge, ethnicity as a factor has not been demonstrated to be predictive of patient tolerance to colonoscopy.

We have observed that conscious sedation in our patients resulted in a hypoxia rate of 6.25% and hypotension rate of 2.8%. Sedation-related cardio-pulmonary complications are known to occur in 0.1 – 1.6% [22-26]; and death in 0 [27] to 0.03%[22,24] according to published Western series'. Possible explanations for differences in our cohort include higher mean doses of midazolam used (compared to published reports) and different population characteristics in our study. We identified increased age, defined as > 65 years, as a risk factor for hypotension, and a prolonged duration of procedure (>30 minutes) as a risk factor for hypoxia. Altered pharmacodynamics that occur with benzodiazepines and opioids in the elderly, coupled with a greater amount of co-morbidity and polypharmacy, are the most probable explanations for the hypotension observed [28]. A prolonged duration might have resulted in more sedation being administered to our patients, although this was not demonstrated in our study (Table IIIa). More likely, hypoxaemia may have resulted by prolonged abdominal distention and pain during colonoscopy, both of which are recognized to impair mechanical ventilation and stimulate vagally-mediated bronchospasm [29]. The poorer tolerance observed in our patients who had a prolonged colonoscopy supports this explanation.

We conclude that the majority of Malaysian patients undergoing sedated colonoscopy with a combination of midazolam and pethidine tolerate it well and have a low cardio-respiratory complication rate. However, we have also demonstrated that almost 1 in 7 adult patients tolerate the procedure poorly, even with conscious sedation. Fifty percent of these patients are unwilling to undergo colonoscopy performed in a similar manner. To improve survival in diseases like colorectal cancer, vast numbers of adults at risk will require screening and surveillance colonoscopy at regular intervals. Our data suggests that such optimal clinical management may not be entirely possible in our population with the current practice of conscious sedation.

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