

Efficacy of Propofol With Midazolam and Meperidine Versus Midazolam and Meperidine for ERCP by Endoscopists with Variable Experience

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Received: December 26, 2013

Revised: April 24, 2014

Accepted: April 30, 2014

Published online: June 21, 2014

ABSTRACT

AIM: Endoscopic retrograde cholangiopancreatography (ERCP) is commonly done with intravenous benzodiazepine and meperidine sedation. Propofol alone or in combination is more effective than conventional sedation. There were limited studies comparing the efficacy of propofol with midazolam and meperidine (PMM) to midazolam and meperidine (MM) in ERCP. This study aim to compare the efficacy and safety of PMM to MM in ERCP by endoscopists with variable experience.

METHODS: A prospective randomized controlled study in 140 patients scheduled for ERCP at a tertiary center was done. Patients were randomized to either PMM (group A, $n=70$), or MM (group B, $n=70$). The induction time, procedure time, recovery time, pain and satisfaction scores, co-operation and complications were recorded. ERCPs were performed by trainees or staffs.

RESULTS: The mean induction time and mean recovery time in group A were shorter than that of group B. ($p=0.00$, $p=0.000$) The mean oxygen saturation reduction and the oxygen desaturation to $< 90\%$ in group A were less than in group B. ($p=0.014$, $p=0.0000$). The mean systolic blood pressure reduction was higher in group A than in Group B. ($p=0.000$). The patient-co-operation was 74.28% in group A and 41.42% in group B. ($p=0.000$). The overall outcomes for trainees and staffs for each group were similar. The adverse events in elderly

were not different from those of younger patients in both groups.

CONCLUSION: PMM was better than MM regarding patient-cooperation, rapid induction and recovery time and less episode of oxygen saturation.

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Key words: Combination sedation; Propofol; Midazolam; Meperidine; ERCP

Netinatsunton N, Attasaranya S, Sottisuporn J, Witeerungrot T, Piratvisuth T, Ovartharnporn B. Efficacy of Propofol With Midazolam and Meperidine Versus Midazolam and Meperidine for ERCP by Variable Experienced Endoscopists. *Journal of Gastroenterology and Hepatology Research* 2014; 3(6): 1121-1126 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/>

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is usually done under conscious sedation with benzodiazepine and meperidine but one-third to one-half of patients experienced ERCP related pain or discomfort^[1,2].

Propofol has recently been widely used for gastrointestinal endoscopy^[1,3,4]. Propofol was better than traditional sedation in terms of short recovery time and good patient cooperation in ERCP in one meta-analysis^[5]. Multiple prospective studies of propofol with variety of sedatives and analgesics in ERCP showed the combination is superior to propofol alone in most studies with similar adverse event rate^[6-8].

There are limited studies comparing combination of propofol with midazolam and meperidine (PMM) with midazolam and meperidine (MM) in ERCP^[9,10]. Balanced PMM sedation provided higher efficacy and safety compared to sedation with MM for therapeutic endoscopy including ERCP in one report^[9]. PMM sedation associated with faster recovery and better patient's satisfaction compared to MM sedation for ERCP with similar safety profile in another study^[10]. Propofol was given as bolus in one study but by infusion in another^[9,10]. Propofol

infusion associated with slower recovery time and a tendency to develop hypotension than propofol bolus injection^[11]. In both studies, the procedures were performed by experienced endoscopists^[9,10]. Our study is to compare the efficacy of the combination of intravenous bolus of propofol with midazolam and meperidine versus midazolam and meperidine administered by trained endoscopic nurses under the supervision of the endoscopists in ERCP performed by endoscopists with variable experience.

METHODS

Setting

This was a prospective randomized study conducted at the NKC institute which is a tertiary center for endoscopy, Faculty of Medicine, Prince of Songkla University.

All patients aged more than 18 years scheduled for ERCP at the NKC institute from January 2010 to December 2011 were enrolled. Patients with more than one ERCP done during the study period were enrolled only once. Patients with pregnancy, American Society of Anesthesiologist (ASA) Class IV or V, concomitant emergency situation, respiratory disease, sleep apnea, allergy to egg or soybean, drug abuse and previous history of failed sedation were excluded.

This study was approved by the hospital ethic committee. The informed consent was obtained before the procedure and patient was randomized to either PMM (group A) or MM (group B) by using random numbers generated by a computer in sealed envelopes.

The ERCPs were performed by using a standard Olympus duodenoscope (TJF-160 R/JF-140 R) by 4 trainees under supervision and by 3 experienced endoscopists at our institute. The sedation was administered according to the protocol (below) by an endoscopic nurse under the supervision of the endoscopist who performed the procedure. All the endoscopic nurses had been trained for the administration of propofol by the department of anesthesiology and had attended the compulsory cardiopulmonary resuscitation course in our hospital.

Sedation protocol

Group A. The sedation protocol had been modified from the studies of Seifert *et al*^[7] and Cohen *et al*^[12]. Midazolam 1 mg was given in patients aged < 70 years and 0.5 mg in patients aged ≥ 70 years and meperidine was fixed at 20 mg. Propofol was given as a bolus of 20 mg initially and then 5-10 mg was given every 30-60 seconds to maintain the desired sedation level.

Group B. Midazolam 2-5 mg intravenously (IV) and meperidine 25-50 mg IV were given initially then midazolam 0.5-1.0 mg IV and meperidine 5-10 mg IV were given every 2-3 minutes to maintain the desired sedation level. The midazolam and meperidine dosages were adjusted according to patient's age and health status. This is the standard protocol routinely used at our institute.

The target of Sedation

The target of sedation was moderate to deep sedation based on the ASA levels^[13].

Patient monitoring

Heart rate, respiratory rate and oxygen saturation were continuously monitored by a digital monitor (Phillips V24CT). Blood pressure measurement and visual inspection of the patient were done every 5 minutes. The numbers of oxygen desaturation episode, hypotensive episode and apnea episode were recorded. Nasal oxygen supplement was provided as needed. Flumazenil and naloxone were available as reversal agents when serious adverse events from midazolam and

meperidine developed.

Outcome measurements

The primary outcome was the efficacy assessed by induction time [the time from sedation to endoscope intubation, (IT)], procedure time [the time from endoscope intubation to withdrawal (PT)], recovery time [the time from endoscope withdrawal to full recovery (RT)], the scale of patient's co-operation (PCP) (1=poor, 2=fair, 3=acceptable, 4=good, 5=excellent) rated by the endoscopist, the scale of patient's grading of pain using visual analog scale (PP) (0-10) and patient's satisfaction (PS) (1=unacceptable, 2=extremely uncomfortable, 3=slightly uncomfortable, 4=no discomfort).

The secondary outcome was the safety profile assessed by desaturation [oxygen saturation < 90 % at least 10 second (OD)], hypotension (systolic blood pressure (SBP) < 90 mmHg or dropped more than 25 % of baseline), bradycardia (heart rate < 50 beats/min) and apnea (cessation of respiration > 10 seconds).

The procedure was terminated if oxygen saturation < 90 % not responding to nasal oxygen supplement and tactile stimulation or SBP < 90 mmHg not responding to fluid challenge or heart rate below 50 beats/min or apnea developed.

Post ERCP pancreatitis was defined according to Cotton's criteria^[14].

Recovery Score

Full recovery score was defined as Aldrete score of 10^[15].

Post procedure follow-up

Patients were contacted by phone on day 1, 3 and 30 after the procedure and attended out-patient clinic at 2 weeks.

Statistical Analysis

The categorical data were analyzed by Chi-square test or Fisher's exact test where appropriate and the continuous data were analyzed by Student's t test. A *p*-value of < 0.05 was considered as statistical significance.

RESULTS

One hundred and forty patients with 68 male and 72 female were recruited. Seventy patients were in group A and group B respectively. The baselines characteristics were not significantly different between the two groups regarding age, sex ratio, body mass index, ASA class, alcohol usage, smoking, sedatives usage, prior difficult sedation and indications for ERCP. The narcotic and analgesic usages were significantly higher in group A than group B (Table 1).

Efficacy

The mean±SD dosage of propofol was 197.80 ± 120.20 mg in group A and the mean±SD dosage of midazolam and meperidine were 6.94±5.59 and 82.99±38.80 mg respectively in group B. The IT in group A was significantly shorter than in group B. The PT in group A and B were similar. The RT in group A was significantly shorter than in group B (Table 2). The PP score and the number of patient with satisfaction were similar in both groups. The patient co-operation was good to excellent in 67 (95.71%) patients in group A and in 59 (84.28%) patients in group B and the difference was statistically significant (Table 3).

The ERCPs by experienced endoscopists were 11 in group A and 9 in group B. The PT, RT and PP for staffs and for trainees were not significantly different in both groups.

Table 1 Patient characteristics, clinical data and indications for ERCP.

	Group A n=70	Group B n=70	p-value
Age \pm SD (years)	55.77 \pm 17.35	61.3 \pm 16.52	0.052
Sex (Male/Female)	32/38	36/34	0.499
BMI \pm SD	22.94 \pm 5.08	22.88 \pm 4.39	0.946
ASA class			
I	45	31	0.056
II	23	35	
III	2	4	
Alcohol use	15	7	0.063
Smoking	15	9	0.178
Regular sedative use ¹	4	1	0.172
Regular narcotic use ¹	5	0	0.023
Regular analgesic use ¹	8	2	0.049
Prior difficulty with sedation ²	4	3	0.824
Indications for ERCP			
CBD stone	39	42	0.621
Benign biliary stricture	8	8	
Malignant biliary stricture	8	9	
Hilar CCA	8	8	
PD stone removal/stent insertion	5	2	
Bile leakage/pancreatic leakage	2	0	

¹ Regular usage for at least 1 week. ² Complications occurred in previous sedation. BMI: body mass index; PD: pancreatic duct; CCA: Cholangiocarcinoma.

Table 2 The mean medication dosage, the mean induction time, mean procedure time and mean recovery time.

	Group A n=70	Group B n=70	p-value
Mean propofol dosage \pm SD (mg) (range)	197.80 \pm 120.20 (40-580)		
Mean midazolam dosage \pm SD (mg) (range) ¹		6.94 \pm 5.59 (1-45)	
Mean meperidine dosage \pm SD (mg) (range) ¹		82.99 \pm 38.80 (6-200)	
Mean induction time \pm SD (minutes) (range)	3.94 \pm 2.18 (1-11)	5.47 \pm 2.51 (2-11)	0.000
Mean procedure time \pm SD (minutes) (range)	40.67 \pm 27.50 (7-158)	43.24 \pm 31.35 (10-200)	0.618
Mean recovery time \pm SD (minutes) (range)	24.71 \pm 23.03 (0-95)	88.50 \pm 54.62 (10-240)	0.000

¹ Fixed dosage per protocol.

Table 3 Patient's VAS pain score, patient satisfaction and cooperation.

	Group A n=70	Group B n=70	p-value
Mean pain score \pm SD (VAS)	0.249 \pm 0.69	0.371 \pm 1.16	0.413
Patient assessment of satisfaction			
Unacceptable	0	0	
Extremely uncomfortable	0	1	
Slightly uncomfortable	8	11	
No discomfort	62	58	0.516
Endoscopist assessment of cooperation			
Poor	0	0	
Fair	1	1	
Acceptable	2	10	
Good	15	30	
Excellent	52	29	0.000

VAS: visual analog scale.

Adverse events

The numbers of oxygen saturation <80%, hypotension and bradycardia were not significantly different between the two groups. The mean percent reduction in oxygen saturation compared to baseline value was significant greater in group B than group A. OD in group A was significantly lower than group B. However, the desaturation episodes were transient and were corrected by nasal oxygen supplement. The mean percent reduction in SBP in group A

was significantly more than that of group B but the number of patients with SBP less than 90 mmHg in each group was similar. One patient in group A developed a short episode of apnea and the procedure was terminated but after manual assisted bag ventilation, spontaneous respiration was restored and the procedure was continued until finish. The sedation related adverse events for patients aged <70 years and patients aged \geq 70 years in group A and B were similar (Table 4). Fifteen of 18 patients aged >70 in group A and 22 of 26 patients aged >70 in group B had sedation related adverse events but the difference was statistically not significant (Chi's square, $p=0.76$).

Mild post ERCP pancreatitis occurred in 3 (4%) in group A and in 2 (3%) in group B which was not significantly different.

The sedation related complications rates in patients with ERCP by staffs compared with ERCP by trainees in group A and B were statistically not significant (Table 5).

The ERCP related complications for the experienced endoscopists and trainees were not significantly different in both groups.

DISCUSSION

PMM was more effective than MM in terms of short IT, PCP and shorter RT. Our results are comparable to previous studies of propofol-based sedation for endoscopic procedures^[16-24]. The efficacy of PMM may be explained by a more rapid onset of action and more rapid recovery of propofol compared to other sedative agents.

Intermittent bolus dose of propofol can be precisely titrated to achieve conscious sedation and was superior to infusion regarding more rapid RT and a less tendency of developing hypotension^[11]. The efficacy of PMM by propofol bolus injection compared with PMM by propofol infusion in ERCP remains to be evaluated. The mean dosage of propofol was 197.80 \pm 120.20 mg and it was lower than in most series using propofol alone^[17,19,21,25,26]. The outcome of the present study is comparable to those of two other studies^[9,10]. However, in our study, the endoscopists had variable experience in ERCP. Nonetheless, the overall outcome for trainees and staffs was not significantly different but further study with a larger number may clarify this. The propofol dosage in our study was higher than Lee study but it was similar to Angsuwatcharakon study. The lower dosage in Lee study may be explained by the lower target of sedation.

Our study showed the higher incidence of desaturation and the greater reduction in mean oxygen saturation in group B and the significant reduction in mean systolic blood pressure in group A, however all the complications were not clinically critical. In addition, there was no significant difference in the rate of serious cardiorespiratory complications between the 2 groups. Lee and Angsuwatcharakon found a higher incidence of desaturation in cocktail sedation than with conventional sedation (Table 6). The rate of desaturation was higher in this study than Lee study but was similar to Angsuwatcharakon study. This may be due to no prophylactic oxygen supplementation was routinely given. Oxygen supplementation and a lower sedation target may minimize desaturation in ERCP with conscious sedation. The mean procedure time in our study was similar to Lee study but this is not comparable since study of Lee included different procedures. The procedure time reported by Angsuwatcharakon *et al* with ERCPs performed by experienced endoscopist was less than in our study. This may be explained by the different skills of the endoscopists performing the procedure.

The safety profile of PMM in elderly patients was comparable to that in younger patients in this study but further studies specifically comparing PMM in elderly and younger patients are warranted to

Table 4 Baseline and adverse cardiorespiratory parameters of the whole both groups and adverse cardiorespiratory parameters of subgroups of patients aged < 70 and ≥70 years.

	Group A (n=70)	Group B (n=70)	p-value
Baseline oxygen saturation ± SD (%)	98.00 ± 1.76	97.3 ± 2.49	0.044
Mean% decrease in oxygen saturation + SD	1.01% ± 5.86%	1.72% ± 4.18%	0.014
No. of patient with any episode of oxygen saturation lower < 90% (%)	26 (37.1%)	40 (57.1%)	0.027
No of patient with any episode of oxygen saturation < 80% (%)	5 (7%)	3 (4%)	0.718
Mean baseline SBP ± SD (mmHg)	139.1 ± 27.6	147.1 ± 33.4	0.124
Mean% decrease in SBP ± SD (mmHg)	13.6% ± 34.3%	2.8% ± 29.3%	0.000
No. of patient with any episode of SBP < 90 mmHg (%)	12 (17.1%)	14 (20%)	0.828
Mean baseline heart rate ± SD (bpm)	83.1 ± 14.7	88.4 ± 18.8	0.066
No. of patient with HR < 50 bpm	1	0	1.000
No. of patient with interrupted procedure due to adverse event	1	0	1.000
Subgroup by age			
	Age < 70	Age ≥ 70	p-value
Group A	52	18	
No. of patient with any episode of oxygen saturation < 90%	16	10	0.064
No. of patient with any episode of oxygen saturation < 80%	4	1	0.756
No. of patient with any episode of SBP < 90 mmHg	8	4	0.516
Total with adverse events	28	15	0.053
Group B	44	26	
No. of patient with any episode of oxygen saturation < 90%	26	14	0.669
No. of patient with any episode of oxygen saturation < 80%	2	1	0.888
No. of patient with any episode of SBP < 80 mmHg	7	7	0.272
Total with adverse events	35	22	0.834

HR: heart rate; bpm: beat per minute.

Table 5 Adverse cardiorespiratory events during ERCP by experienced endoscopists and trainees.

	Experience endoscopist	Trainee	p-value
Group A	11	59	
No. of patient with any episode of oxygen saturation < 90%	7	19	0.085
No. of patient with any episode of oxygen saturation < 80%	1	4	1.000
No. of patient with any episode of SBP < 90 mmHg	0	12	0.190
Group B	9	61	
No. of patient with any episode of oxygen saturation < 90%	4	36	0.483
No. of patient with any episode of oxygen saturation < 80%	0	3	1.000
No. of patient with any episode of SBP < 80 mmHg	1	12	0.190

Table 6 Studies evaluating PMM and MM in ERCP.

Author	Patients	Propofol group	Meperidine / Midazolam	p-value
Lee CK <i>et al</i> ^[9]	Propofol dosage (mg)	106.86 ± 105.02		
	O ₂ saturation <90%	5.9%	2.9%	NS
	SBP <90 mmHg	2.9%	1.9%	NS
	HR below 50 bpm	0%	0.96%	NS
	Transient interruption of procedure	2.9%	0%	NS
	Total procedure time	51.15 ± 28.95	57.20 ± 45.55	NS
Angsuwatcharakon P <i>et al</i> ^[10]	Propofol dosage (mg)	172.08 ± 92.15		
	O ₂ saturation <90%	58.3%	31.4%	<0.001
	O ₂ saturation <85%	8.7%	1.0%	0.019
	Mean % decrease in O ₂ saturation	8.7% (6.9%)	6.7% (6.1%)	0.026
	SBP decrease ≥25% baseline	26.2%	22.5%	NS
	SBP <90 mmHg	13.6%	4.9%	NS
	HR decrease ≥25% baseline	23.3%	17.6%	NS
	HR below 50 bpm	1%	0%	NS
Total procedure time	27.88 ± 14.38	31.60 ± 17.56	NS	
Present study	Propofol dosage (mg)	197.80 ± 120.20		
	O ₂ saturation <90%	37.1%	57.1 %	0.027
	O ₂ saturation <80%	7%	4%	NS
	Mean% decrease in O ₂ saturation	1.01% (5.86%)	1.72% (4.18%)	0.014
	SBP <90 mmHg	17.1 %	20 %	NS
	Mean % decrease in SBP	13.6% (34.3%)	2.8% (29.3%)	0.000
	HR below 50 bpm	0.01%	0%	NS
Total procedure time	40.67 ± 27.50	43.24 ± 31.35	NS	

HR: heart rate; bpm: beat per minute.

make a firm conclusion.

Our study was unique in term of reflecting the real life ERCP practice. However, there were some limitations that included a single center study, a small number of patients recruited, and un-blinded investigators regarding the sedation protocol.

The vast difference of regimens of propofol based sedation and different population recruited in the studies reported in the literature

make the comparison of these data difficult. Further studies with a standardized regimen in similar patients groups to assess the efficacy and safety of propofol based sedation may help to clarify the role of propofol in endoscopic procedures.

Although the safety profile of propofol based-sedation in ERCP was comparable to conventional sedation, however serious adverse events associated with propofol do occur. This underscored the

necessity for well-trained personnel in providing the sedation and careful patient monitoring^[20].

CONCLUSION

The PMM was better than MM in terms of cooperation, rapid recovery time, without an increase of serious cardiorespiratory events.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Faculty of Medicine, Prince of Songkla University. The authors thank Prof. Alan for the assistance with the statistical analysis and all the nurses at NKC institute in administration of the study medications, monitoring and taking care of patients during and after the procedures. Authors' contributions: NN participated in the design of the study, patient recruitment, randomization, performing ERCP and manuscript preparation. SA, JS, and TW participated in patient recruitment and performed the ERCP procedures. BO participated in patient recruitment, performed ERCP and assisted in the manuscript preparation.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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