Moderate and deep nurse-administered propofol sedation is safe

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ABSTRACT

INTRODUCTION: Non-anaesthesiologist-administered propofol sedation (NAPS/NAAP) is increasingly used in many countries. Most regimens aim for light or moderate sedation. Little evidence on safety of deep NAPS sedation is available. The aim of this study was to explore the safety of intermittent deep sedation with NAPS in patients undergoing gastroenterologic endoscopic procedures.

METHODS: This was a retrospective case-control study. All patients sedated with NAPS for colonoscopies, sigmoidoscopies and oesophagogastroduodenoscopies from May 2007 through December 2012 were included. Cases were defined as patients developing an adverse event (oxygen saturation < 92%, a drop in mean arterial pressure of > 30% or a drop in systolic blood pressure of > 50 mmHg). The remaining patients served as controls.

RESULTS: A total of 6,840 consecutive patients undergoing 7,364 procedures were included. The mean propofol dose was 331.6 mg (standard deviation = 179.4 mg). The overall rate of hypoxia was 3.2%, and the rate of hypotension was 3.1%. Assisted ventilation was needed in 0.5%. Age (p < 0.001), American Society of Anesthesiologists (ASA) class 3 (p = 0.017) and total propofol dose (p = 0.001) were associated with a higher rate of adverse events.

CONCLUSION: Safety during intermittent deep sedation with NAPS was good. Age, ASA class 3 and total propofol dose were correlated with a higher rate of adverse events. Patients aged 60 years or more needed more handling during adverse events.

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Data on light and moderate propofol sedation administered by non-anaesthesiologists (NAAP or NAPS) during gastrointestinal (GI) endoscopy compared with traditional sedatives have been collected over the years [1]. Furthermore, large cohort studies document few or no adverse events, high patient satisfaction and good working conditions during moderate propofol sedation [2, 3]. But propofol-induced deep sedation during GI endoscopy is poorly documented.

Research on the optimal setup for NAPS is still readily conducted and published, and the mounting evidence on administration strategy, patient selection, nurse education and monitoring standards is implemented in guidelines [4, 5]. The evidence collected so far indicates that American Society of Anesthesiologists (ASA) class 3 or higher, age and emergency endoscopy seem to correlate with a higher rate of adverse events [3]. Various modes of administration such as a manually controlled infusion pump and target-controlled infusion are being investigated; the latter seemingly provides a higher cardiopulmonary stability [6, 7]. Most endoscopy-directed regimens aim for light or moderate sedation in which the patient is able to respond to verbal commands. For deeper sedation, little evidence on safety is available [8, 9], and the administration is often left to anaesthesiologists. An age-adjusted intermittent bolus strategy has been successfully used in our unit since 2007 for 7,343 colonoscopies, sigmoidoscopies and oesophagogastroduodenoscopies (EGD). NAPS was initially implemented to achieve moderate sedation for all non-emergency GI endoscopies in ASA class 1, 2 and 3 patients. How-ever, deep sedation was achieved intermittently in almost all patients. Parts of data from the first 2,656 patients have previously been published [10].

The aim of this retrospective study was to explore the safety of intermittent deep sedation with propofol administered by nurses in selected patients undergoing upper and lower GI endoscopic procedures.

METHODS
Ethics
The study was approved by the Capital Region Ethics Committee (No: H-4-2013-171) and the National Data Protection Agency (No: HEH-2013-077).

Design
All patients sedated with NAPS for colonoscopies, sigmoidoscopies and EGDs from the implementation of the method in May 2007 through December 2012 were included and retrospectively evaluated in a case control design. Cases were defined as patients developing an adverse event (hypoxia or hypotension) as a dichotomous outcome (0 or 1). The remaining patients served as controls.

TABLE 1

Baseline demographics.

Patients/procedures, n	6,840/7,364
Age, yrs (N = 6,821)	
Mean (SD)	59.8 (17.8)
Median	63.0
Sex, n (%) (N = 6,840)	
Male	2,641 (38.6)
Female	4,199 (61.4)
ASA class, n (N = 6,810)	
1	2,114 (30.9)
2	4,304 (62.9)
3	392 (5.7)
Procedure[a], n (%)	
Upper endoscopy	2,487 (36.4)
Lower endoscopy	4,340 (63.6)
EGD	2,487 (33.8)
Colonoscopy	4,477 (60.8)
Sigmoidoscopy	400 (5.4)
Sedation	
Propofol dose, mg (N = 6,806):	
Mean (SD)	331.6 (179.4)
Median	290.0
Sedation time, min (N = 5,495):	
Mean	24.6 (24.6)
Median	20.0
Infusion rate, mg/min (N = 5,485):	
Mean (SD)	20.9 (19.6)
Median	15.0

ASA = American Society of Anesthesiologists; EGD = oesophagogastro-duodenoscopy; N: patients with available data; SD = standard deviation.
a) A total of 524 patients had > 1 procedure performed and were registered according to their primary procedure.

Patients
The NAPS inclusion criteria were age ≥ 13 years and fasting prior to procedure: 2 h for fluids and 6 h for solids.

The exclusion criteria were ASA classification > 2, but currently stable ASA class 3 patients with none or few physical limitations were allowed and included. Furthermore, patients with allergy against soy/egg/peanuts, sleep apnoea, a history of anaesthesia complications, body mass index > 35 kg/m², pregnancy, difficult airway and massive ventricular retention were excluded along with all emergency endoscopies.

Propofol administration
The designated nurse administered propofol according to an age-adjusted regimen. The induction bolus in milligrams (mg) was calculated as 100 minus the patient's age in years , but with a maximum of 60 mg. After 45-60 sec., a subsequent bolus corresponding to half of the induction bolus (maximum 30 mg) could be administered if needed. The desired level of sedation was maintained with a refract bolus of 10-20 mg in case of patient move-ment (extremities, eyebrows or noise) or every 1-2 min if the patient was cardiopulmonary stable as assessed by the nurse (sufficient depth and frequency of respiration and stable circulation). Depth of sedation was not registered routinely. The desired level of sedation was a sleeping patient with no spontaneous movement who was unresponsive to endoscopic and normal verbal stimulation throughout the procedure corresponding to deep sedation. Supplemental oxygen was delivered through a nasal cannula at 3 l/min, and saline infusion administered intravenously (IV) at a rate of 500 ml/h.

Adverse events handling
With the current guideline, originally developed by Walker et al [11], propofol was administered by a dedicated endoscopy nurse supervised by the endoscopist. Adverse events were usually handled by the nurse, but the team was mobilised early if needed. Both had completed a two-and-a-half-day theoretical workshop and simulation-based course with a multiple choice exam available at the Danish Institute for Medical Simulation. Prior to unsupervised procedures, physicians have to complete one day of supervised sedations. Nurses have to complete 4-6 weeks of bedside observation and supervised training, gradually working more independently. All adverse events were treated with withdrawal of propofol, increased oxygen flow (5-7 l/min) and saline flow (2 l/min) until the patient was less sedated. Airway obstruction was treated with chin lift and jaw thrust and, if needed, with airway devices. In case of apnoea > 30 s, assisted ventilation was initiated. Laryngospasm and threatening laryngospasm were treated with lidocaine 25-50 mg IV and, if not resolved, with assisted ventilation. Circulatory depression was treated with Trendelenburg´s position and, if needed, ephedrine 5-10 mg. Anaesthesia staff were not present, but could be called upon at all times.

Data items
The data collected before and during sedation were: age, sex, ASA class, procedure type, total propofol dose, the occurrence and duration of an adverse event (oxygen saturation (SAT%) < 92%, a drop in mean arterial pressure (MAP) of > 30% or a drop in systolic blood pressure (SBP) of > 50 mmHg from baseline), and the intervention used to resolve an adverse event (increased oxygen, airway devices, assisted ventilation, rescue drug) how the event was handled. After the initial 2,000 procedures, sedation time was also registered.

Statistical analysis
Statistical data analysis was performed using IBM SPSS version 19. The primary safety outcome was the occurrence of an adverse event. A risk factor analysis of base-

line data was made with logistic regression, chi-squared with Bonferroni correction, independent samples T-test or Mann-Whitney as appropriate. A subgroup analysis of cases (with adverse event) in terms of handling was also performed with logistic regression.

Trial registration: not relevant.

RESULTS

A total of 6,840 consecutive patients undergoing 7,364 procedures were included for evaluation. The desired depth of sedation was achieved in all but one patient in whom the procedure was incomplete due to insufficient sedation. The mean propofol dose was 331.6 mg (SD: 179.4 mg), and the mean infusion rate was 20.9 mg/min (SD: 19.6 mg/min). Baseline demographics are depicted in **Table 1**. The overall rate of hypoxia was 3.2%, and the rate of hypotension was 3.1%. Assisted ventilation was needed in 0.5%. Age ($p < 0.001$), ASA class 3 ($p = 0.017$) and total propofol dose ($p = 0.001$) were associated with a higher rate of adverse events as seen in **Table 2**. Furthermore, an increased risk of hypoxia was found during EGD ($p = 0.001$), but there was no increased risk of hypoxia associated with stable ASA class 3 ($p = 0.961$). Hypotension was found more frequently during colonoscopy ($p = 0.001$) and ASA class 3. Analysing the age groups shown in **Table 3** (< 40 years, 40-60 years and > 60 years), we found that higher age group was associated with a greater risk of an adverse event, but also with a

Bolus administration of propofol by non-anaesthesia staff.

greater need for respiratory ($p < 0.001$) and circulatory support ($p < 0.001$) in the occurrence of an adverse event, as seen in Table 3, despite a significant decrease in propofol dose ($p < 0.001$). An anaesthesiologist was called upon six times due to bradycardia (n = 1) during colonoscopy, hypoxia during gastroscopy (n = 4) and hypoxia during colonoscopy (n = 1). One patient was intubated due to excessive coughing. The remaining five patients were stabilised before arrival of the anaesthesiologist, and all procedures were resumed.

TABLE 2

	Hypoxia			Drop in blood pressure			Overall
	no	yes	p-value[a]	no	yes	p-value[a]	p-value[a]
Patients, N (%)	6,626	214 (3.2)		6,636	204 (3.1)		
Age, yrs, mean (n)	59.6 (6,607)	65.8 (214)	> 0.001	59.5 (6,618)	69.6 (203)	> 0.001	> 0.001
Sex, N (%)							
Male	2,555	86 (3.3)	0.878	2,543	98 (3.7)	0.053	0.119
Female	4,071	128 (3.0)		4,093	106 (2.5)		
ASA class, n (%)							
1	2,065	48 (2.3)		2,078	35 (1.7)		
2	4,155	149 (3.5)	0.961	4,169	135 (3.1)	0.002	0.017
3	375	17 (4.3)		360	32 (8.2)		
Procedure, n (%)							
Upper endoscopy	2,399	101 (4.0)	> 0.001	2,442	58 (2.3)	0.007	0.318
Lower endoscopy	4,227	113 (2.6)		4,194	146 (3.5)		
EGD	1,906	80 (4.0)		1,944	42 (2.1)		
Colonoscopy	4,347	130 (2.9)	0.001	4,323	154 (3.4)	0.001	0.071
Sigmoidoscopy	373	4 (1.1)		369	8 (2.1)		
Sedation, mean (n)							
Propofol dose, mg	331.4 (6,599)	339.1 (207)	0.015	330.6 (6,607)	363.8 (199)	0.001	0.001
Sedation time, min	24.6 (5,335)	25.9 (160)	0.805	24.7 (5,367)	22.9 (128)	0.477	0.612
Infusion rate, mg/min	20.9 (5,326)	20.2 (159)	0.575	20.8 (5,357)	23.4 (128)	0.725	0.714

ASA = American Society of Anesthesiologists; EGD = oesophagogastroduodenoscopy; n: patients with available data.
a) Logistic regression.

Adverse events.

DISCUSSION

We found that the intermittent use of deep sedation during NAPS is a safe method. The current regimen caused 6.6% of the population to experience some sort of adverse event; most of the events observed were minor and self-resolving and none of them compromised safety. The mean propofol dose was 331.6 mg and the mean infusion rate was 20.9 mg/min. The overall rate of hypoxia was 3.2% and the rate of hypotension was 3.1%. As previously demonstrated [3], age, ASA class 3 and total propofol dose were predictors of an increased risk of developing an adverse event despite the age-adjusted regimen. Upper endoscopy was an independent predictor for hypoxia as seen in other studies [2], but the increased risk of hypotension in patients undergoing colonoscopy has not previously been described. Overall,

there was no procedure-correlated risk. Another finding was that age over 60 years was correlated with a more frequent need for respiratory and circulatory support during an adverse event.

Training

The nurse training programme seems comparable with that of other similar institutions [12, 13] with a supervision period ranging from 2-8 weeks. Some units have a shorter training period [14], and some have no dedicated sedation nurse [15] but report a frequency of hypoxia (1.4-2.3%) and a frequency of assisted ventilation (0.02-0.14%) comparable to those who have [11, 12] (0.1-6.7% and 0-0.05%) and a lower frequency of these complications than demonstrated in this report (hypoxia: 3.2%, assisted ventilation: 0.5%).

TABLE 3

Adverse event handling in age groups. The values are n (%).

Age group	No event	Airway support	Trendelenburg	Assisted ventilation	Ephedrine	Total	p-value
Hypoxia							
< 40 yrs	1,045 (99.7)	3 (0.3)	–	0 (0)	–	1,048	
40-60 yrs	1,868 (98.0)	26 (1.4)	–	13 (0.7)	–	1,907	< 0.001
> 60 yrs	3,682 (95.9)	133 (3.5)	–	26 (0.7)	–	3,841	
Total	6,595 (97.0)	162 (2.4)	–	39 (0.6)	–	6,796	
Drop in blood pressure							
< 40 yrs	1,040 (99.2)	–	1 (0.1)	–	7 (0.7)	1,048	
40-60 yrs	1,893 (99.3)	–	5 (0.3)	–	9 (0.5)	1,907	< 0.001
> 60 yrs	3,762 (97.9)	–	39 (1.0)	–	40 (1.0)	3,841	
Total	6,695 (98.5)	–	45 (0.7)	–	56 (0.8)	6,796	

TABLE 4

Airway management in other studies.

Reference	Patients, n	Frequency of O_2 saturation < 90%, %	Propofol dose, mean, mg (SD) [range]	Mask ventilation, n (%)	Intubation, n
[2] Rex et al	646,080	–	–	489 (0.1)	11 (4 died)
[11] Walker et al	9,152	0.1	150 [30-500][a] 210 [40-860][b]	5 (0.05)	0
[12] Tohda et al	27,500	6.7	72 (10.2)[a] 94 (12.8)[b]	0 (0)	0
[13] Rex et al (3 centres)	12,481	0.19	303 (166)	24 (0.02)	0
	13,834	0.09	212 (93)	12 (0.09)	0
	10,402	0.12	132 (97)	13 (0.12)	0
[14] Sieg	3,610	1.4	119 (39)	5 (0.14)	0
[15] Külling et al	27,061	2.3	161 [50-650][a] 116 [30-500][b]	6 (0.02)	0
[16] Horiuchi et al	2,101	0.2	96.4 (27)	0	0
[17] Sipe et al	40	2.5	218	0 (0)	0
[18] Rex et al	2,000	0.5	238 [30-940]	4 (0.2)	0
[19] Sipe et al	100	8[c]	90 (40)	0 (0)	0

SD = standard deviation.
a) Upper endoscopy.
b) Lower endoscopy.
c) No O_2 administration.

Administration

Different ways of administration, such as continuous pump infusion or target-controlled infusion, are being investigated. Presently, these modalities are mainly used by anaesthesiologists for advanced endoscopies. The preferred mode of administration with NAPS seems to be bolus administration. Agreement on the used bolus regimen is fairly good and in accordance with this report. In all the studies in **Table 4**, induction with propofol was achieved with 20-60 mg adjusted for weight [4] or age [11-13, 16] or a combination. All the depicted studies used refract boluses of 10-20 mg for maintenance. Under the assumption that the referred studies have a comparable procedure distribution (colonoscopy and EGD) and length of procedure, the differences in the mean total propofol dose (range of means 72-303 mg and 332 mg in this study) are likely found in the frequency of administration. The objective of sedation in our unit is to achieve a calm working environment, amnesia and patients who never move or grimace as a sign of pain or discomfort. Furthermore, the aim is to avoid the excitatory state which is likely to induce laryngospasm during gagging or coughing. To achieve this objective, deep sedation is needed and obtained through more frequent dosing. A previous study of NAPS for deep sedation during upper GI endoscopies used a mean infusion rate of 8.2 mg/min with an infusion pump system [9]. A sample of studies aiming for moderate sedation reported total propofol doses of 94 mg [12], 119 ± 39 mg [14], 174 ± 125 mg [20], 303 ± 166 mg/212 ± 93 mg/132 ± 97 mg [13]. The infusion rate (20.9 mg/min) and the mean total dose (331.6 mg) in the present study indicate that the sedation was more deep than moderate. In fact, we have failed to identify any reports of higher propofol doses.

Adverse events

We consider respiratory failure to be the most important adverse event during propofol sedation. Anaesthesiologic assistance was called for on six occasions. All six adverse events except for one (due to excessive coughing) were readily reversed by the endoscopy team before arrival of the anaesthesiologist and, hence, not considered serious. The only non-hypoxic adverse event was bradycardia, and this was probably not induced by the sedation, but by reflex during colonoscopy. Propofol has a narrow therapeutic interval and no antidote other than the context-sensitive half-life, which is short (2-4 minutes). This pharmacodynamic profile demands competency in the management of obstructed airways and apnoea. In the studies presented in Table 4, the frequency of hypoxia < 90% SAT ranged from 0-8.3% (2.1% in the present study) and mask ventilation ranged from 0-0.4% (0.5% in the present study) during sedation with

a wide range of mean propofol doses. All the studies reported good patient compliance and a high level of satisfaction. This emphasises several issues. Firstly, with an event in 1 of 50 and assisted ventilation in less than 1 of 200, or never, airway management competency must be maintained through recertification or training of some sort. Our unit has used annual training days in the anaesthesia department, practicing assisted ventilation with a face mask. Secondly, elderly patients seem to have more need for airway manipulation when hypoxic, and they should be sedated carefully and by experienced staff. Thirdly, with nearly the same choice of propofol doses, but a quite different total propofol consumption, all the studies reports of good results and relatively small differences in adverse event rates, despite the expected dose-response. So the therapeutic window of propofol seems wider than previously assumed. Therefore, with educated endoscopy teams and well-established exclusion criteria, a wider range of sedation depth can be applied, depending on the patient or the procedure needs. Whereas evidence on light and moderate sedation is considerable, more evidence on indications, training and setup requirements for deep sedation with NAPS is warranted.

Limitations

Assessment of sedation depth at five-minute intervals or with a bispectral index monitor would have been valuable in a report on the use of deep sedation. However, a review of the literature reveals no studies on sedation during endoscopy using the same high total doses of propofol. One study [8] documented that 19% of sedations with a more conservative propofol regimen, supplemented with fentanyl, were deep sedations. On the basis of our observations, we feel that it is safe to say that deep sedation was achieved in all of the procedures. Hence, the term "intermittent deep sedation" is appropriate. Another limitation to this study is the lack of reporting of the lowest measured oxygen saturation. When discussing safety, this measurement would have been valuable.

CONCLUSION

The frequency of adverse events during intermittent deep sedation was comparable to that of moderate sedation. Age, ASA class 3 and total propofol dose were correlated with a higher rate of adverse events. Patients aged 60 years or more needed more handling during the occurrence of an adverse event. Hypotension was more frequent during colonoscopy.

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