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Respiratory Complications in Outpatient Endoscopy with Endoscopist-Directed Sedation

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ABSTRACT

Background & Aims: Respiratory complications represent an important adverse event of endoscopic procedures. We screened for respiratory complications after endoscopic procedures using a questionnaire and followed-up patients suggestive of respiratory infection.

Method: In this prospective observational, multicenter study performed in Outpatient practices of gastroenterology we investigated 15,690 patients by questionnaires administered 24 hours after the endoscopic procedure.

Results: 832 of the 15,690 patients stated at least one respiratory symptom after the endoscopic procedure: 829 patients reported coughing (5.28%), 23 fever (0.15%) and 116 shortness of breath (SOB, 0.74%); 130 of the 832 patients showed at least two concomitant respiratory symptoms (107 coughing + SOB, 17 coughing + fever, 6 coughing + coexisting fever + SOB) and 126 patients were followed-up to assess their respiratory complaints. Twenty-nine patients (follow-up: 22.31%, whole sample: 0.18%) reported signs of clinically evident respiratory infection and 15 patients (follow-up: 11.54%; whole sample: 0.1%) received therefore antibiotic treatment. Coughing or vomiting during the endoscopic procedure resulted in a 156.12-fold increased risk of respiratory complications (95% CI: 67.44 - 361.40) and 520.87-fold increased risk of requiring antibiotic treatment (95% CI: 178.01 - 1524.05). All patients of the follow-up sample who coughed or vomited during endoscopy developed clinically evident signs of respiratory infection and required antibiotic treatment while this occurred in a significantly lower proportion of patients without these symptoms (17.1% and 5.1%, respectively).

Conclusions: We demonstrated that respiratory complications following endoscopic sedation are of comparably high incidence and we identified major predictors of aspiration pneumonia which could influence future surveillance strategies after endoscopic procedures.

Key words: endoscopist-directed propofol sedation – respiratory complications – pulmonary infection – outpatient endoscopy .

INTRODUCTION

Several studies investigating endoscopist-directed propofol sedation (EDP) reported extremely low incidences of cardiovascular events during endoscopic procedures [1-6]. We believe that another important, yet long-time underestimated adverse event associated with endoscopic sedation are respiratory complications. A study from Italy reported that 18 out of 17,542 patients received antibiotic treatment for aspiration during endoscopy, which resulted in significant episodes of oxygen desaturation [7]. It is presumed that deeper levels of sedation lead to diminished airway protective reflexes and thus increase the risk of aspiration pneumonia [8]. In a retrospective population-based study, Cooper and colleagues [9] reported that aspiration pneumonia occurred in 0.10–0.14% of colonoscopies. It has been hypothesized that coughing during endoscopy might be a surrogate marker for increased risk of aspiration-related postprocedural infection [8]. Although it seems reasonable that most episodes of postprocedural pulmonary infection would be associated with intraprocedural coughing or coughing during the period of sedation, this relationship has not been established to date.

To our knowledge, there exists no prospective study investigating the incidence of respiratory complications after routine endoscopic procedures. Similarly, predictive factors/

surrogate markers for respiratory complications following endoscopy are still unknown. Therefore, we initiated this prospective, multicenter study to investigate the incidence of respiratory complications associated with EDP.

METHODS

The study was approved by the Ethics Committee of the University of Heidelberg, Germany and was conducted from January to July 2013. The study was carried out in accordance with the Declaration of Helsinki in its present form and written consent was obtained from all participating patients. Fifty-three medical practices throughout Germany participated in the study. The practices performed documentation of patient ID, age and sex, the kind of endoscopic procedure, the amount of propofol and midazolam medication administered, the documentation of adverse events including severe coughing or vomiting during the endoscopic procedure.

Inclusion criteria were: age older than 18; patient scheduled for esophagogastroduodenoscopy (EGD), colonoscopy or double examination with or without polypectomy; ASA class I and II or III if non-cardiac cause; completion of the questionnaire investigating respiratory complications.

Exclusion criteria were: age below 18; pregnancy; ASA class III of cardiac cause, or ASA class IV; advanced therapeutic endoscopy (ERCP, papillotomy, stenting, balloon dilatation etc.), morbid obesity, severe sleep apnea and difficult airway anatomy (short neck); allergy to propofol or soy oil.

Sedation regimen

Propofol was administered by intermittent intravenous bolus titration to the necessary level of moderate to deep sedation as clinically judged by the practice nurse and the endoscopist [21]. Overall, 30-50 mg of propofol was applied at the beginning of the endoscopic procedure followed by single boluses of 20-30 mg based on sedation depth. For a sedation regimen consisting of propofol and midazolam, 2-3 mg of midazolam was applied together with 10-20 mg propofol, followed by single propofol boluses of 20-30 mg based on sedation depth. The decision of the sedation regimen carried out was based on individual preference/judgment of the treating physician for each patient. Absolute dosages were adjusted individually according to age, weight, comorbidity and medication. Depth of sedation was not quantified by modified observer's assessment of alertness/sedation scale. The sedation regimen was carried out according to the S3-guideline of the DGVS [10]. For a detailed description of the methods section see Sieg et al [2].

Patient questionnaire and pulmonary infection

Twenty-four hours after the endoscopic procedure the patients were invited to answer a questionnaire. Questions included overall well-being the day after the examination and in comparison to the previous day. Furthermore, patients were asked to report the occurrence of coughing, fever and shortness of breath (SOB). Patients reporting two or more concomitant respiratory symptoms after 24 hours (coughing + fever, coughing + SOB, fever + SOB, coughing + fever + SOB) were classified as having "respiratory complications" based on study protocol and followed-up to investigate the outcome of the respiratory symptoms.

Follow-up

Follow-up was performed via telephone interview investigating the antibiotic treatment, hospitalization, further impairment due to the respiratory complications, smoking status, preexisting pulmonary disorders, and duration of pulmonary symptoms. Patients complaining of persistent concomitant respiratory symptoms up to 72 hours following the endoscopic procedure were classified as having "respiratory complications suspicious of infection".

Statistical analysis

Logistic regression analyses were conducted to address the main effects of endoscopic procedure (colonoscopy vs. gastroscopy vs. colonoscopy and gastroscopy) and sedation (propofol vs. propofol and midazolam) and their interaction on the occurrence of respiratory complications/infections. Correlation analysis was performed using the Pearson correlation coefficient. Additionally, logistic regressions were used to investigate whether the occurrence of coughing or vomiting during the endoscopic procedure is predictive of respiratory complications/infection. Statistics were performed using the SPSS software version 21.0.

RESULTS

We analyzed the questionnaires of 15,690 patients who had received outpatient endoscopy 24 hours prior to questionnaire completion. The study population consisted of 6,660 men and 9,030 women with a mean age of 59 years (SD = 14.2; range 18 to 94 years). A total of 9,174 colonoscopies, 3,878 EGDs and 2,638 double examinations were performed; 7,582 of the patients received propofol mono-sedation and 8,108 received a combination of midazolam and propofol. Propofol and midazolam dosages administered during the examinations and patient characteristics are shown in Table I.

Answers to the questionnaire

Eight hundred and thirty-two of the 15,690 patients stated at least one respiratory symptom after the endoscopic procedure; 829 patients reported newly developed coughing (5.28%), 23 patients fever (0.15%) and 116 SOB (0.74%) the day after the endoscopic examination (Table II). One hundred and thirty patients (0.83%) complained of at least two concomitant respiratory symptoms and were therefore classified as having "respiratory complications". Of these, 107 patients indicated coughing and SOB (82.31%), 17 coughing with concomitant fever (13.08%) and 6 coughing with coexisting fever and SOB (4.62%). Respiratory complications were less frequent in patients in whom colonoscopy was performed (0.58%; n=53) as compared to those who underwent EGD (1.57%, n=61) and similarly frequent in patients that had underwent double examination (0.61%; n = 16, $p < 0.0001$, Table II). Most importantly, this pattern was more pronounced for patients who had received propofol monosedation as compared to a combined sedation regimen of propofol and midazolam (propofol mono: 0.45% colonoscopy, 1.93% EGD, 0.70% double

Table I. Patients' characteristics and medication used for sedation

	Colonoscopy	EGD	Combined examination	Total
Patients (n)	9,174	3,878	2,638	15,690
Women (n)	5,137	2,501	1,392	9,030
Men (n)	4,037	1,377	1,246	6,660
Age years, Mean (SD)	61 (12.8)	55 (16.3)	58 (14.6)	59 (14.2)
Propofol monosedation (n)	4,258	2,331	993	7,582
Propofol + Midazolam (n)	4,916	1,547	1,645	8,108
Dosage Propofol mono Mean (SD) (mg)	149.1 (67.6)	122.2 (43.6)	243.9 (91.8)	153.2 (75.1)
Dosage Propofol (P) + Midazolam (M) Mean (SD) (mg)	P: 88.2 (71.1) M: 2.9 (1.6)	P: 88.9 (56.6) M: 2.5 (1.6)	P: 127.1 (89.5) M: 3.9 (2.0)	P: 96.2 (74.4) M: 3.0 (1.8)

EGD: esophagogastroduodenoscopy

examination; propofol and midazolam: 0.69% colonoscopy, 1.03% EGD, 0.55% double examination; p=0.03). The main effect of sedation was non-significant, p=0.13. Patients classified with respiratory complications also stated reduced overall well-being and we observed a highly significant negative correlation between respiratory complications and well-being (r=-0.10, p=0.00001) (Table III).

Selective follow-up of patients with respiratory complications

We selectively followed-up patients diagnosed with respiratory complications (n=130) as identified by the questionnaire (Table IV). Follow-up was completed in 126 of the 130 patients while we were unable to contact 4 patients who were therefore excluded from further analysis. Twenty-eight of the 126 follow-up patients were active smokers (20.0 pack years, SD=5.77) and 12 patients reported a preexisting pulmonary disorder (chronic obstructive pulmonary disease in 10 patients and bronchial asthma in 2 patients). All patients with an underlying pulmonary disorder developed the investigated respiratory symptoms after the endoscopic procedure and recalled subjective well-being (without these symptoms) prior to the endoscopic examination.

Twenty-nine patients (follow-up: 22.31%; whole sample: 0.18%) reported signs of respiratory complications suspicious of infection as they mentioned a newly developed fever, coughing and SOB up to 72 hours following the endoscopic procedure and were therefore classified accordingly. Fifteen patients (follow-up: 11.54%, whole sample 0.10%) received antibiotic treatment by their treating physician for their respiratory symptoms. No patient needed to be hospitalized as a result of respiratory complications or had persistent impairment at the end of the study.

With respect to the whole sample, respiratory complications suspicious of infection were less frequent in patients that had received colonoscopy (0.13%) compared to EGD (0.31%, p=0.05) and comparably frequent in patients that had received a double examination (0.19%, p=0.38). Neither the type of sedative, nor the interaction between the type of sedative and endoscopic procedure were significant, $p > 0.41$. Importantly, symptoms indicating aspiration pneumonia solely developed after the endoscopic procedure and showed no correlation with smoking (n = 126: r= 0.12, p=0.20) and underlying pulmonary disorders (n=126: r = -0.05, p = 0.59).

Coughing and vomiting during EDP

The treating gastroenterologists were asked to report the occurrence of adverse events [2] including coughing or vomiting during the endoscopic procedure. Severe coughing was observed in 49 patients (0.31%) and vomiting in 6 patients (0.04%). Coughing was significantly more frequent with increasing dosages of propofol (Pearson correlation coefficient r= 0.064; p<0.0001) and decreasing dosages of midazolam (r= -0.042; p<0.0001). The correlation with age was non-significant (r= -0.008; p=0.35). All correlations between vomiting and total dosage of propofol, total dosage of midazolam, or age were non-significant, rs< 0.007, ps >0.41.

Table II. Incidence of pulmonary symptoms based on endoscopic procedure and sedation

	Propofol			Propofol + Midazolam		
	Colonoscopy n (%)	EGD n (%)	Combined n (%)	Colonoscopy n (%)	EGD n (%)	Combined n (%)
Coughing	150 (3.5%)	208 (8.9%)	62 (6.2%)	227 (4.6%)	109 (7.0%)	73 (4.4%)
Shortness of breath	18 (0.4%)	43 (1.8%)	6 (0.6%)	30 (0.6%)	13 (0.8%)	6 (0.4%)
Fever	4 (0.1%)	3 (0.1%)	1 (0.1%)	8 (0.2%)	4 (0.3%)	3 (0.2%)
Respiratory complications	19 (0.4%)	45 (1.9%)	7 (0.7%)	34 (0.7%)	16 (1.0%)	9 (0.5%)
Respiratory complications suspicious of infection						
Whole sample	7 (0.2%)	10 (0.4%)	3 (0.3%)	5 (0.1%)	2 (0.1%)	2 (0.1%)
Follow-up-sample	36.8%	23.3%	50.0%	15.2%	12.5%	22.2%

EGD: esophagogastroduodenoscopy

Table III. Characteristics of the patients with and without respiratory complications (n= 15,690)

	Respiratory complications	No respiratory complications	p value
Sex n (%)			
Female	80 (0.9%)	8,950 (99.1%)	0.36
Male	50 (0.8%)	6,610 (99.2%)	
Age years (SD)	62 (14.8)	60 (14.2)	0.09
Propofol sedation (mg)	139.1 (77.2)	153.4 (75.0)	0.11
Propofol + midazolam sedation (mg)	P: 92.1 (84.0) M: 2.6 (1.6)	P: 96.2 (74.4) M: 3.0 (1.8)	0.72 0.07
Overall well-being (questionnaire)	5.1 (2.4)	7.2 (1.9)	0.00001

Table IV. Characteristics of the patients with and without respiratory complications suspicious of infection (n=126)

	Respiratory complications	No respiratory complications	p value
Sex n (%)			
Female	19 (24.4%)	59 (75.6%)	0.65
Male	10 (20.8%)	38 (79.2%)	
Age years, Mean (SD)	64 (12.3)	62 (15.5)	0.45
Overall well-being n (SD) (questionnaire)	4.2 (2.3)	5.4 (2.3)	0.02
Smokers n (%)	yes: 9 (32.1%) no: 20 (20.4%)	yes: 19 (67.9%) no: 78 (79.6%)	0.19
Preexisting pulmonary disorders n (%)	yes: 2 (16.7%) no: 27 (23.7%)	yes: 10 (83.3%) no: 87 (76.3%)	0.58
Propofol sedation n (SD)	168.0 (107.0)	124.5 (57.4)	0 .03
Propofol + midazolam sedation n (SD)	P: 140.0 (158.7) M: 3.2 (1.8)	P: 85.6 (61.2) M: 2.4 (1.5)	0.08 0.21
Antibiotic treatment n (%)	yes: 14 (48.3%) no: 15 (51.7%)	yes: 1 (1.0%) no: 96 (99.0%)	<0.0001

Risk factors for respiratory complications

When screening for factors associated with the occurrence of respiratory complications, coughing or vomiting during the endoscopic procedure were identified as being the key risk factors. Coughing or vomiting during endoscopy resulted in a 156.12-fold increased relative risk of developing respiratory complications suspicious of infection the day after the examination (95%CI: 67.44 - 361.40) and increased the risk of pulmonary symptoms requiring antibiotic treatment by 520.87 (95%CI: 178.01 - 1524.05). With respect to the follow-up sample, respiratory complications suspicious of infection occurred in 100% of the patients who coughed or vomited during the endoscopic procedure and in 17.1% of the patients who did not show these symptoms. Similarly, all patients who received antibiotic treatment coughed or vomited during the endoscopic procedure.

DISCUSSION

Respiratory complications represent a serious complication following endoscopic procedures [7, 11, 12] although most likely often unrecognized in clinical practice. So far, the incidence of respiratory complications has not been prospectively investigated and there exists no information on surrogate markers. To address these issues, we initiated a prospective, multicenter study in outpatient practices of gastroenterology.

Using a questionnaire, we screened for the occurrence of pulmonary symptoms following endoscopic procedures in 15,690 patients. One hundred and thirty (0.83%) of the 15,690 patients included in the present study complained of at least two respiratory symptoms (fever, coughing or SOB) 24 hours after the endoscopic procedure. To diminish self-limiting unspecific pulmonary reaction following endoscopic procedures from clinically evident respiratory infection, we followed up these patients. Interestingly, 29 of the 126 patients reported concomitant fever, coughing and SOB up to 72 hours after the endoscopic procedure, in accordance with signs of clinically evident respiratory infection. As these symptoms solely developed after the endoscopic procedure and showed no relationship with smoking or underlying pulmonary disorders, we suspect that these respiratory complications are due to infection. Fifteen patients received antibiotic treatment for management of their respiratory symptoms while no patient needed to be hospitalized. Overall, the incidence of respiratory complications suspicious of infection was mostly attributed to patients who had received EGD compared to patients with colonoscopy or double examination. This is in accordance with a former study showing prolonged coughing co-occurring in 3% of the patients during non-emergent endoscopic procedures, in particular EGD [8]. A recent study performed in Italy found an incidence of aspiration following colonoscopy of 0.16%, making pulmonary aspiration the most common significant complication of colonoscopy in that series [7]. Our results are consistent with the Italian study, indicating that respiratory complications are a very important consequence, though likely often unrecognized in clinical practice. An evaluation of complications related to

sedation in the U.S. Medicare population found that the use of anesthesiologist services was associated with an increased risk of aspiration pneumonia [9]. Since the anesthesiologist services are an excellent surrogate for the use of propofol in the U.S., these data indicate that respiratory infection is associated with a greater depth of sedation. Our results are consistent with this observation, since we found a substantial risk of respiratory complications associated with the use of EDP. Although the risk of respiratory complications was the highest for EGD, it is interesting that it remained comparable when evaluating colonoscopy (0.58%) to combined examinations (EGD + colonoscopy, 0.61%). As EGD was performed first in combined examinations, we hypothesize that the emptying of gastric contents during EGD might be an explanation of this phenomenon.

During screening for risk factors associated with the development of respiratory complications, we were able to identify severe coughing or vomiting during the procedure to be of a major predictive value. Severe coughing or vomiting during the endoscopic procedure was associated with an increased relative risk of respiratory complications suspicious of infection of 156.12 (95%CI: 67.44- 361.40) and an increased risk of respiratory infection requiring antibiotic treatment of 520.87 (95%CI: 178.01- 1524.05). To our knowledge, this is the first study directly linking coughing/vomiting during endoscopy to clinically respiratory complications/antibiotic treatment.

We recognize several potential limitations of the study. Most importantly, the diagnosis of respiratory complications/infection was not based on radiologic imaging or laboratory markers but on the presence of clinical symptoms. Additionally, patients were only followed up when complaining of at least two pulmonary symptoms in order to increase sensitivity of the questionnaire; this may result in an underreported incidence of respiratory complications.

CONCLUSION

Our data indicate that patients with severe coughing or vomiting during endoscopic procedures should be informed about the risk of subsequent respiratory symptoms and fever, and that they may require medical attention including antibiotics. Whether these patients might benefit from prophylactic antibiotics is unknown.

Conflicts of interest: There exists no conflict of interest for the authors mentioned above. The Berufsverband Niedergelassener Gastroenterologen (bng) and Germany and Pentax Europe Incorp., Hamburg, Germany funded the study.

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