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# A survey among Flemish gastroenterologists about endoscopic sedation practices in colorectal cancer screening

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#### Abstract

Background & study aims: The sedation levels and methods used for colonoscopy in colorectal cancer screening programs vary from country to country and from continent to continent. Little is known in the literature about how frequently the different sedation levels are used in colorectal cancer screening colonoscopies. We made a survey among all Flemish gastroenterologists (GI) to determine how frequently they use the different sedation modalities in this target population and to determine the motives of the GI to opt for one or another sedation modality.

Patient and methods: An online survey was sent to all 329 Flemish GI by e-mail. A reminder e-mail was sent one month later. Participants could indicate how frequently (by percentage) they used the different sedation methods (no sedation, minimal sedation, conscious sedation, deep sedation) and which sedative medication they administered. In addition, they were asked to indicate their main motives for choosing a specific sedation method. Descriptive statistics were used.

*Results:* 112 out of 329 GI answered the questionnaire (response rate 34%). Anesthesia monitored care is the most frequently used sedation modality, followed by conscious sedation. Patient preference is the main motive for most GI to use each sedation modality.

*Conclusions:* Anesthesia monitored care is currently the most frequently used sedation regimen to perform a colonoscopy in the FIT positive population or in the colorectal cancer screening program in Flanders. The motives given by the GI for choosing one or another sedation modality are not always congruent with current scientific evidence or guidelines. (Acta gastroenterol. belg., 2023, 86, 527-532).

Keywords: colonoscopy, sedation practices, colorectal cancer screening, water exchange, anesthesia monitored care.

## Introduction

Colonoscopy is the gold standard for detection and treatment of premalignant colonic polyps. To minimize patient discomfort during the procedure, colonoscopies are often performed under sedation (1). Sedation types vary from minimal sedation or anxiolysis over moderate or conscious sedation to deep sedation. The different modalities are often categorized according to the sedation level score of the American Society of Anesthesiologists (table 1) (2). Minimal sedation is achieved by administration of a minimal dose of benzodiazepines (most frequently 2-2.5 mg midazolam intravenously), conscious sedation by using somewhat higher dosages of benzodiazepines alone or in combination with opioids. For deep sedation, the combination of higher dose benzodiazepines/opioids or propofol are used. Deep sedation with propofol is usually performed by an anesthesia team (anesthesiologist and nurse anesthesist),

also called anesthesia monitored care (AMC). Deep sedation with midazolam/opioids is most frequently self-administered by the gastroenterologist (GI).

The sedation levels and the medication used for sedation vary from country to country and from continent to continent (3). Little is known in the literature about how frequently the different sedation levels are used in colorectal cancer screening colonoscopies.

We made a survey among all Flemish GI to determine how frequently they use the different sedation modalities in this target population. A second part of the survey was to determine the motives of the GI to opt for one or another sedation modality.

# Materials and methods

## Study characteristics

In February 2023, an online survey was sent to all 329 Flemish gastroenterologists by e-mail. A reminder e-mail was sent one month later.

#### Questionnaire

A brief introduction clarified the purpose of the analysis, specifically that the survey concerned colonoscopic examinations carried out in the context of colorectal cancer screening (screening colonoscopy or FIT positive population). It was clearly stated that the survey was anonymous and that the results would be used for scientific purposes only.

First, participants could indicate how frequently (by percentage) they used the different sedation methods (no sedation, minimal sedation, conscious sedation, deep sedation) and which sedative medication they administered. In addition, they were asked to indicate on the questionnaire their main motives for choosing a specific sedation method, and to indicate in order the main motives that determined their choice (to choose between: quality of procedure, patient preference, patient

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Sedation level	Minimal sedation (anxiolysis)	Moderate (conscious) sedation	Deep sedation	General anesthesia	
Responsiveness	Normal	Verbal or tactile stimuli	Repeated painful stimuli	Unresponsive to painful stimuli	
Airway	Normal	No intervention required	Intervention may be required	Intervention usually required	
Spontaneous ventilation	Normal	Adequate	May be inadequate	Usually inadequate	
Cardiovascular function	Normal	Normal	Usually maintained	May be impaired	

Table 1. — Sedation levels modified from the American Society of Anesthesiologists (ASA)



Figure 1. — Percentage of responding GI using a specific type of sedation in more than 50% or in all colonoscopies.

satisfaction after the procedure, efficiency, center's habit, safety of the procedure or other motives).

## Analysis

Descriptive statistics were used.

First, the proportion of GI (in %) using a specific type of endoscopic sedation was calculated. The proportion of GI (in %) using a specific type of endoscopic sedation in at least 50% of colonoscopies and in 100% of colonoscopies was also calculated.

Secondly, to obtain a percentage of how often each sedation modality is used on average by the GI, the sum of all percentages for the specific sedation modalities were taken together and divided by the number of responding GI.

Thirdly, the proportion of GI (in %) indicating a particular motive as the most important reason to use a specific type of sedation was calculated.

#### Results

112 out of 329 Flemish gastroenterologists answered the questionnaire (response rate 34%).

– Deep sedation: 93.0% of the GI use deep sedation, 84.8% of the GI use AMC deep sedation and 1.8% of the gastroenterologists self-administer propofol. 27.7% of the GI state to use AMC deep sedation as their only sedation type. 60.7% used AMC in at least 50% of the colonoscopies. Only 2.7% of the GI use deep sedation with self-administered combination of higher dose of benzodiazepines/opioids in at least 50% of all colonoscopies (fig. 1).

– <u>Conscious sedation</u>: 50.0% of the GI use conscious sedation and 21.4% of the GI use conscious sedation in at least 50% of all colonoscopies, only 1.8% of GI state to use conscious sedation as their only sedation type.

 <u>Minimal sedation</u>: 35.7% of the GI use minimal sedation and only 2.7% of the GI use minimal sedation in at least 50% of the colonoscopies.

 <u>No sedation</u>: 50.9% of the GI perform colonoscopy without sedation, only 1.8% of the GI perform colonoscopy without sedation in at least 50% of the colonoscopies.

A majority (63.4%) of the GI perform colonoscopy under deep sedation in more than 50% of all colono-



- Deep sedation with propofol by gastroenterologist (0,002%)
- = Deep sedation with higher doses benzodiazepines/opioids by gastroenterologist (5,7%)
- Conscious sedation (23,5%)
- Minimal sedation (5,1%)
- No sedation (4,2%)

Figure 2. — The frequency of each sedation modality used by the responding GI (if we assume that all GI perform more or less the same number of diagnostic colonoscopies).

scopies. The responding GI use on average deep sedation in 67,1% of the colonoscopies they perform, mainly with AMC in 61.4%, followed by conscious sedation in 23.5% of colonoscopies (fig. 2).

The most important motive to choose for one or another sedation modality was also reported (table 2).

- <u>Deep sedation</u>: patient preference was the main motive of the GI to choose for AMC (24.2%) and for non-AMC deep sedation with benzodiazepines/ opioids (45.0%). 19.2% of the gastroenterologists mentioned quality of the colonoscopy as the main motive for choosing AMC, and in 17.2% center's habit was the main motive for AMC. For 19.4% of GI, efficiency was the main reason to choose benzodiazepines and/or opioids.

- <u>Conscious sedation</u>: patient preference was the main motive of the GI to choose for conscious sedation (33.3%), followed by center's habit (18.5%) and safety of the procedure (16.7%)

- <u>Minimal sedation</u>: patient preference was the main motive of the GI to choose for minimal sedation (42.9%), followed by safety of the procedure (31.0%) and quality of the procedure and center's habit (both 7.1%). - <u>No sedation</u>: patient preference was the main motive of the GI to choose for no sedation (75.0%), followed by safety of the procedure (8.9%) and quality of the procedure (7.1%).

# Discussion

This is the first electronic web survey providing data about sedation practice for colonoscopies performed for colorectal cancer screening in Flanders.

The response rate (RR) was 34%, comparable to the 38% RR and 47% RR in a Greek survey and the 41% RR in an Italian survey, but lower than the 72% RR in a Swiss survey and the 65% RR in a Spanish survey (4,5,6,7).

The results of this survey confirm that the sedation methods and sedation levels vary widely from endoscopist to endoscopist. The responding GI use on average deep sedation in 67,1% of the colonoscopies they perform, mainly with AMC in 61,4% (10 times more frequent than deep sedation with benzodiazepines/opioids self-administered by the GI), conscious sedation in 23,5%, minimal sedation in 5,1% and no sedation in 4,2%. 27.7% of the GI exclusively use propofol AMC while 15.2% never use propofol AMC. However, we have no data on the absolute numbers of colonoscopies performed in Flanders under propofol, AMC or conscious sedation as the annual number of colonoscopies performed by each responding GI was not recorded.

This survey shows that propofol is the most frequently used sedation medication, in line with results of other surveys in Europe. In a German survey, 78.7% of the GI mentioned propofol (monotherapy or in combination with benzodiazepines) as the most frequently used sedation regimen, while only 9% of the GI never used propofol. Sedation with propofol was only in 2% by AMC as most propofol sedations were low dose regimens and were supervised by a trained nursing staff and not by an anesthesiologist (8). In a Spanish survey propofol was used in 80% of the colonoscopies (9).

In contrast to this, in a recent nationwide survey in Greece midazolam was the most frequently used sedative agent, with over 90% of GI using midazolam as monotherapy or in combination with other drugs (4) A

Sedation modality	Quality of procedure (ADR; PDR)	Patient preference	Patient satisfaction after procedure	Efficiency	Center's habit	Safety of procedure	Other motive		
Anesthesia monitored care (AMC)	19.2	24.2	15.2	9.1	17.2	11.1	4.0		
Deep sedation with higher doses benzodiazepines/opioids by gastroenterologist	6.5	45.2	6.5	19.4	9.7	3.2	9.7		
Conscious sedation	3.7	33.3	9.3	13.0	18.5	16.7	5.6		
Minimal sedation	7.1	42.9	2.4	4.8	7.1	31.0	4.8		
No sedation	7.1	75.0	3.6	1.8	1.8	8.9	1.8		
ADR= adenoma detection rate; PDR= polyp detection rate.									

Table 2. — Percentage of GI's reporting a particular motive as most important motive to use a sedation modality

prospective cohort study (from 2008 to 2011) in the USA identified 3168228 colonoscopy procedures with 34.4% of colonoscopies performed with anesthesia services (10). A recent survey among specialists from different countries showed that gastroenterologists in France used deep sedation in 76% of patients, and in the USA in 53% of patients (it was not mentioned what medication was used to achieve deep sedation). Conscious sedation was general practice for 86% of patients in Germany and for 76% of patients in UK. In Japan 58% of patients had no sedation at all (11). Presumably, those differences reflect many different factors including availability of AMC, waiting lists, costs, health care systems and regulations, rather than just the personal choice of the GI or the patient's preference.

How are the results of our survey positioned to scientific guidelines and recommendations?

The majority of Flemish GI use deep sedation (most frequently AMC) for diagnostic colonoscopies and only a minority perform the procedures under minimal or conscious sedation. Colorectal cancer screening colonoscopies are considered as non-complex endoscopic procedures. The European Society of Gastrointestinal Endoscopy (ESGE) stated in their guideline that noncomplex endoscopic procedures can be performed under moderate sedation, maintaining a high degree of patient satisfaction (12). The American Society of Gastrointestinal Endoscopy (ASGE) stated that the combination of an opioid and benzodiazepine is a safe and effective regimen for achieving minimal to moderate sedation for colonoscopy in patients without risk factors for sedation-related adverse events (13).

Patient preference was the main motive of the GI to choose for a specific sedation modality, as well for AMC as for conscious or minimal sedation. The main reason why patients choose AMC is presumably the fear of pain during the colonoscopy and fear of procedural awareness. Deep sedation with propofol resulted in the best pain control during the procedure but the differences were small (about 10%) compared to non-propofol sedation in a questionnaire filled in by 22725 patients after colonoscopy (14). In this analysis, the endoscopist was the most important modifiable factor associated with pain during colonoscopy, suggesting a wide variety in the skills of the GI practitioners. 90% of the pain during a colonoscopy occurs during the insertion phase (15). Dynamic position changes and water-aided insertion techniques (water immersion and water exchange) significantly reduce insertion pain and improve patient's experience during unsedated or minimally sedated colonoscopy (16, 17, 18). We hypothesize that the small satisfaction benefits in favor of deep sedation with propofol might disappear using these techniques (14).

The quality of the procedure was the main motive for 19% of the gastroenterologists to use AMC. There is no convincing scientific evidence supporting this motive. The adenoma detection rate (ADR), polyp detection rate (PDR) and the cecal intubation rate (CIR) are

most frequently used as objective quality parameters for colonoscopies. The use of sedation (compared to no sedation) did not increase ADR or PDR in an older Austrian study (published in 2012) of 52506 screening colonoscopies (19). A comparable ADR and PDR was seen in a recent meta-analysis comparing propofol sedation with opioid/benzodiazepine sedation (20).

Changing the patient's position during colonoscopy (dynamic position change) reduces the insertion pain and augments ADR, but this is difficult in deeply sedated patients (21). ASGE stated in a recently published guideline that dynamic changes in patient position may increase ADR by up to 7 percentage points (22). Sedation compared to no sedation showed a slightly higher cecal intubation rate of 1-3% (95.82% CIR with sedation; 94.31% CIR without sedation).<sup>19</sup> In recent studies with water-aided insertion techniques the cecal intubation rate is +/- 95% even in unsedated or at most conscious sedated patients (23,24).

Center's habit was the third most frequently mentioned motive by the GI to use both AMC and conscious sedation. Presumably, the availability of an anesthesia team, free beds at the day clinic and the business model of the hospital and/or the endoscopy unit could play a role in choosing for AMC. Certain centers perform almost all colonoscopies by using AMC and 28% of the responding Flemish GI exclusively use AMC. In these centers the patient probably cannot choose one or another sedation modality. The British Society of Gastroenterology stated that every patient should be able to choose for one or another sedation modality after being informed correctly about the different sedation options (25). A recent panel of 32 Canadian multidisciplinary participants recommended to not mandate the use of deep sedation for routine colonoscopy (26).

Efficiency was a minor motive to choose a specific type of sedation in this survey. Cecal intubation time (CIT) and CIR can be used as efficiency parameters. When comparing sedation with no sedation, cecal intubation rate increased by 1-3% in sedated patients in an older study (19). A systematic review comparing propofol sedation with benzodiazepine/opioid sedation also showed a slightly higher cecal intubation rate in the propofol sedation group (RR 1.02, 95% CI 1.00-1.03) (20). In recent studies with water-aided insertion techniques the cecal intubation rate is around 95% even in unsedated or at most conscious sedated patients (23,24). The CIT in deeply sedated AMC patients is 2-4 minutes lower than in unsedated or minimal sedated patients, but the differences become smaller with better insertion techniques and higher experience of the endoscopist (23).

Safety of the procedure was an important motive for Flemish GI to use conscious sedation as well as minimal or no sedation. 11% of the GI also provided safety of the procedure as main motive to use AMC. In literature, different studies show a small but significantly higher complication risk when using AMC. In a populationbased study in the USA of 165527 colonoscopies including 35128 procedures with AMC, a significantly higher risk of aspiration was documented compared to colonoscopies without AMC (27). In a Canadian population-based cohort study with 3059045 outpatient colonoscopies, anesthesia assistance was significantly associated with an increased risk of aspiration pneumonia (28).Another prospective cohort study in the USA included 3168228 colonoscopies of which 34.4% were conducted with anesthesia services. A 13% higher risk of any complication (perforation, stroke, anesthesia related complication) was found in the group receiving anesthesia service (10).

# Limitations

The questionnaire was answered by 112 gastroenterologists on a total of 329. We should be aware that those 112 respondents could not sufficiently represent all the Flemish gastroenterologists.

Gastroenterologists were asked to answer the use of different sedation types used in percentages. As such, we could not draw conclusions about absolute numbers of colonoscopies.

Motives to choose a specific type of sedation were predefined. It is possible that those predefined motives did not reflect all possible motives. For example, a shorter waiting list could be a motive to choose a particular type of sedation.

We don't know if all gastroenterologists in their center are able to offer all sedation modalities to the patients.

Patient preference was the main motive of the GI to choose for all types of sedation, however we don't know if all the different types of sedation are explained to the patients before scheduling a colonoscopy. We also don't know if the patients always have the free choice for choosing one or another sedation modality.

# Conclusion

AMC is currently the most used sedation regimen to perform a colonoscopy in the FIT positive population or in colorectal cancer screening program in Flanders. This trend is also seen in neighboring countries. The motives given by the Flemish gastroenterologists for choosing one or another sedation modality are not always congruent with current scientific evidence or guidelines. Probably deep sedation and propofol AMC are overused as it concerns non-complex endoscopic procedures. The patients should have the choice between the different sedation modalities in every center. The motive for choosing deep sedation with propofol AMC for safety or quality reasons is not supported by scientific evidence (on the contrary for safety). Safety should be the primary key factor rather than the speed of the procedure or the personal preference of the individual endoscopist.

## Author contribution

SA and GD were responsible for conception and design of the article. SA and GD were involved in the analysis of the data. All authors were involved in interpreting the data and drafting the article. All authors read and approved the article.

## **Conflict of interest**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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#### References

- ZHAO, S., DENG, X. L., WANG, L. *et al.* The impact of sedation on quality metrics of colonoscopy: a single-center experience of 48,838 procedures. *Int. J. Colorectal Dis.* 35, 1155-1161 (2020).
- American Society of Anesthesiologists. Distinguishing Monitored Anesthesia Care ("MAC") from Moderate Sedation/Analgesia (Conscious Sedation). (Approved by the ASA House of Delegates on October 27, 2004). http:// www.asahq.org/For-Healthcare-Professionals/Standards-Guidelines-and-Statements.aspx Accessed April 22, 2008
- FANTI, L., GEMMA, M., ROSSI, G. *et al.* Sedation and Monitoring for Gastrointestinal Endoscopy: Worldwide Attitudes and Evidence. *Austin J. Gastroenterol.* 2, 1030 (2015).
- PROTOPAPAS, A. A., STOURNARAS, E., NEOKOSMIDIS, G. et al. Endoscopic sedation practices of Greek gastroenterologists: A nationwide survey. Ann. Gastroenterol. 33, 366-373 (2020).
- FANTI, L., AGOSTONI, M., GEMMA, M. *et al.* Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig. liver Dis.* 43, 726-730 (2011).
- HEUSS, L. T., FROEHLICH, F. & BEGLINGER, C. Changing patterns of sedation and monitoring practice during endoscopy: Results of a nationwide survey in Switzerland. *Endoscopy* 37, 161-166 (2005).
- BAUDET, J. S., BORQUE, P., BORJA, E. *et al.* Use of sedation in gastrointestinal endoscopy: A nationwide survey in Spain. *Eur. J. Gastroenterol. Hepatol.* 21, 882-888 (2009).
- RIPHAUS, A., GEIST, F. & WEHRMANN, T. Endoscopic sedation and monitoring practice in Germany: Re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. Z. Gastroenterol. 51, 1082-1088 (2013).
- LUCENDO, A. J., GONZALEZ-HUIX, F., TENIAS, J. M. et al. Gastrointestinal endoscopy sedation and monitoring practices in Spain: A nationwide survey in the year 2014. Endoscopy 47, 383-390 (2015).
- WERNLI, K. J., BRENNER, A. T., RUTTER, C. M. *et al.* Risks Associated With Anesthesia Services During Colonoscopy. *Gastroenterology* **150**, 888-894 (2016).
- AUDIBERT, C., PERLAKY, A. & GLASS, D. Global perspective on colonoscopy use for colorectal cancer screening: A multi-country survey of practicing colonoscopists. *Contemp. Clin. Trials Commun.* 7, 116-121 (2017).
- DUMONCEAU, J. M., RIPHAUS, A., SCHREIBER, F. et al. Nonanesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline - Updated June 2015. Endoscopy 47, 1175-1189 (2015).
- EARLY, D. S., LIGHTDALE, J. R., VARGO, J. J. et al. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest. Endosc.* 87, 327-337 (2018).
- BUGAJSKI, M., WIESZCZY, P., HOFF, G. *et al.* Modifiable factors associated with patient-reported pain during and after screening colonoscopy. *Gut* 67, 1958-1964 (2018).

- LEUNG, J. W., THAI, A., YEN, A. *et al.* Magnetic endoscope imaging (ScopeGuide) elucidates the mechanism of action of the pain-alleviating impact of water exchange colonoscopy - attenuation of loop formation. *J. Interv. Gastroenterol.* 2, 142-146 (2012).
- HSIEH, Y. H., TSENG, C. W., KOO, M. *et al.* Feasibility of sedation on demand in Taiwan using water exchange and air insufflation: A randomized controlled trial. *J. Gastroenterol. Hepatol.* 35, 256-262 (2020).
- ZHAO, S., YANG, X., MENG, Q. *et al.* Impact of the supine position versus left horizontal position on colonoscopy insertion: a 2-center, randomized controlled trial. *Gastrointest. Endosc.* 89, 1193-1201.e1 (2019).
- CADONI, S., FALT, P., GALLITTU, P. et al. Water Exchange Is the Least Painful Colonoscope Insertion Technique and Increases Completion of Unsedated Colonoscopy. *Clin. Gastroenterol. Hepatol.* 13, 1972-1980 (2015).
- BANNERT, C., REINHART, K., DUNKLER, D. et al. Sedation in screening colonoscopy: Impact on quality indicators and complications. Am. J. Gastroenterol. 107, 1837-1848 (2012).
- AZIZ, M., WEISSMAN, S., FATIMA, R. *et al.* Impact of propofol sedation versus opioid/benzodiazepine sedation on colonoscopy outcomes: a systematic review with meta-analysis. *Endosc. Int. Open* 08, E701-E707 (2020).
- LI, P., MA, B., GONG, S., *et al.* Effect of dynamic position changes during colonoscope withdrawal: a meta-analysis of randomized controlled trials. *Surg. Endosc.* 35, 1171-1181 (2021).

- SHAUKAT, A., TUSKEY, A., RAO, V. L. *et al.* Interventions to improve adenoma detection rates for colonoscopy. *Gastrointest. Endosc.* 96, 171-183 (2022).
- LIU, C., ZHENG, S., GAO, H. *et al.* Minimal water exchange by the air-water valve versus left water exchange in unsedated colonoscopy: A randomized controlled trial. *Endoscopy.* 55, 324-331 (2022).
- CADONI, S., FALT, P., RONDONOTTI, E. et al. Water exchange for screening colonoscopy increases adenoma detection rate: A multicenter, double-blinded, randomized controlled trial. *Endoscopy* 49, 456-467 (2017).
- REES, C. J., TREBBLE, T. T., VON WAGNER, C. *et al.* British Society of Gastroenterology position statement on patient experience of GI endoscopy. *Gut* 69, 1718-1719 (2020).
- DOSSA, F., DUBÉ, C., TINMOUTH, J. et al. Practice recommendations for the use of sedation in routine hospital-based colonoscopy. BMJ Open Gastroenterol. 7, (2020).
- COOPER, G. S., KOU, T. D. & REX, D. K. Complications following colonoscopy with anesthesia assistance: A population-based analysis. *JAMA Intern. Med.* 173, 551-556 (2013).
- BIELAWSKA, B., HOOKEY, L. C., SUTRADHAR, R. et al. Anesthesia Assistance in Outpatient Colonoscopy and Risk of Aspiration Pneumonia, Bowel Perforation, and Splenic Injury. *Gastroenterology* 154, 77-85.e3 (2018).