Sedation outside the operation room

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ANALGESIA WITHOUT SEDATIVES DURING COLONOSCOPIES: WORTH CONSIDERING?

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ABSTRACT
Screening by colonoscopy is a proven instrument for early diagnosis of colorectal cancer, but often experienced as an uncomfortable procedure. Today, there are two main strategies to facilitate colonoscopy. First, deep sedation, which results in satisfied patients, but increases sedation-associated risks and raises costs for health care providers. Second, there is the advocacy for colonoscopies without any form of sedation. This might be an option for a special group of patients, but does not hold true for everybody.
Following Moerman’s hypothesis: “If pain is the crucial point, why do we need sedation?” this review shows the analgesic options towards a painless procedure, increasing success-rates without increasing risk of sedation. There are two agents with the potential to be a nearly ideal analgesic agent for colonoscopy: alfentanil and nitrous oxide (N₂O). Both substances aim at a comfortable, yet alert patient and facilitate a short turnover combined with a superior safety profile. Besides owning anxiolytic and analgesic characteristics, both drugs show a rapid begin and termination of action and are therefore easy to titrate to reach the aimed level of sedation.
INTRODUCTION

Screening by colonoscopy is a proven instrument for early diagnosis of colorectal cancer. This is an important reason, why colonoscopies belong to the most performed endoscopic procedures. In the Netherlands, there was a 64% increase in colonoscopies from 2004 until 2009. However, motivating patients to participate in colonoscopy screening continues to be a challenge.

The lack of knowledge among patients about the nature of colonoscopy may be an important barrier, limiting patients to accept and undergo such a screening procedure. Commonly, colonoscopy is associated with anxiety and pain. Additionally, patients complain over disruption of normal daily activities by bowel preparation, hangover effects from sedation, and the need for an escort after the procedure. Dominitz et al. stated that 25% of patients who never have had a colonoscopy before are willing to surrender median 90 days of their life to avoid the screening procedure. However, after having had a colonoscopy, this number decreased to almost zero days.

Pain and discomfort during colonoscopy

Activation of sensory nerves by stretching the sigmoid wall due to looping of the coloscope or over-insufflation with air triggers pain that is typical for colonoscopies. This visceral pain often aggravates due to its autonomous components, e.g., sweating, bradycardia, dizziness, hypotension, and nausea.

Pain is not only a physical reaction of the body, but it also has mental and behavioural components associated with former experiences and cultural background, which often seems to be resistant to analgesic treatments. Pain is less tolerated by younger, often slender females and is better accepted in the older generation. Unfortunately, it is yet impossible to predict, how painful the examination for the individual patient will be.

Sedation for colonoscopy

Sedation for colonoscopy is currently a matter of discussion; In the United States (US), sedation has become standard for colonoscopies. Depending on the study, either moderate or deep sedation is favoured. Other parts of the world advocate for completely medication-free colonoscopies.

In one US study, only 16.9% (n=73) patients would accept sedation-free colonoscopy. However, another study reported that in 23% of patients unsedated colonoscopies could be performed with excellent patient satisfaction and acceptable comfort level. Eckardt et al. showed in a study on 2,500 patients, that 95% of all patients could undergo colonoscopy without sedation when experienced colonoscopists and optimal equipment was present. Unfortunately, the authors did not report data on patient satisfaction. Nowadays, use of
new coloscopes, and experienced endoscopists make colonoscopy without sedation possible to a dedicated and motivated group of patients. This finding is supported by Rex et al. Success rates depend on appropriate selection. Young male with an above-average education level, little preprocedural fear, and a personal preference for procedures without sedation are predictors of a successful sedation-free procedure. However, unpredictable individual anatomical situations can result in unacceptable discomfort for the patient and worse procedural conditions for the gastroenterologist. Baudet et al. reported increased complication rates during colonoscopy without the use of sediment (57 vs. 22%; p<0.001).

**MODES OF ANALGO-SEDATION**

Sedation guidelines have universally defined levels of sedation, reaching from moderate to deep sedation. Deep sedation is generally achieved using propofol. Its fast start and end of action allows for a reduced recovery time. Therefore, there is increasing interest in propofol sedation among gastroenterologists. Unfortunately, its therapeutic range is narrow and enhances the risk of sedation related cardiopulmonary events. That’s the reason, why in most parts of the US sedation with propofol by non-anaesthesiologists, is not allowed. The guidelines in different European states concede the use of propofol to trained nurses or endoscopists, who are solely responsible for sedation. However, this permission only concerns moderate, but not deep sedation.

This means deep sedation is more resource intensive because of the need for specialised sediment staff and extended monitoring. The percentage of colonoscopies with anaesthesia professional participation is expected to rise from 23.9% in 2007 to 53.4% by 2015, respectively. In view of this dramatic increase, health insurance companies try to limit payment for sedation delivered by anaesthesia providers. Patients under deep sediment may have impaired spontaneous breathing requiring assistance to keep an open airway. Closed claims analyses of anaesthesia suggest that deep sedation carries high risks for serious complications even with well trained staff. Cote et al. found a percentage of 12.5% sediment related hypoxaemic events during propofol sedations performed by anaesthesia nurses. In a review of over 20,000 reports in the Clinical Outcomes Research Initiative Database, sediment-related events happened in 1.3% of the cases. Respiratory (0.75%) and cardiovascular complications (0.49%), and delayed recovery of psychomotoric function count for the highest rate among all complications. Furthermore, deeply sedated patients are not able to change position from lateral decubitus to supine without assistance, which makes it difficult to manoeuvre the patient during procedure.
Moderate sedation is a drug-induced reduction of cognitive function. Patients could purposefully respond to verbal commands after light tactile stimulation. Respiration is not impaired. Drugs most commonly used for moderate sedation are midazolam (47%), spasmolytics (11%), and other drugs (5%), mostly combined with an analgesic, e.g., opioids (33%). A combination of two or more analgo-sedatives was used in 37% of the performed procedures. This combination provides excellent analgo-sedation during colonoscopy, but increases the risk for more deep sedation and more frequent respiratory depressions. The duration of action of these combinations might last longer than the procedure, resulting in a delayed recovery and discharge from hospital, disrupting normal everyday activities of the patients and actually increasing treatment costs.

**THE IDEAL AGENT**

The properties of an ideal analgesic agent for colonoscopy aim at a comfortable yet alert patient and facilitate a rapid turnover of patients. The ideal sedation drug also implies a superior safety profile, analgesic and optionally anxiolytic effects combined with a fast begin and termination of action, the possibility to titrate to a planned sedation level, a fast recovery, and all of this without the necessity for extra personnel. Following Moerman’s hypothesis “If pain relief is adequate, sedation is no longer being required,” the question arises whether analgo-sedation could be achieved by using analgesics only. Various studies on sedation regimens have been published, but only a few concentrated on analgesic agents solely.  

**Meperidine**

Meperidine is a synthetic analgesic with an onset of effect within 10 to 15 minutes, lasting for 2 hours with a plasma half-life of 3 to 4 hours. Metabolism to normeperidine occurs rapidly. Normeperidine follows a renal excretion with an extended elimination half-life of 17 hours. This pharmacokinetic profile strongly argues against the use of meperidine for relatively short procedures like colonoscopies.

**Fentanyl**

Fentanyl is an opioid, which has a faster recovery profile than meperidine. Onset of action is within 1–2 min, peak effect occurs at 3–5 min, and duration of action ranges between 30–60 min. For colonoscopies, fentanyl is mostly used in a combination with propofol or a benzodiazepine. Only Lazaraki et al. evaluated the efficacy and safety of fentanyl alone (< 0.5 µg/kg, mean 36 µg) in comparison with midazolam (2 mg, mean 4.6 mg). Fentanyl provided more rapid recovery than midazolam combined with a lower mean discomfort (0.4
vs. 1.0) and pain scores (2.59 vs. 4.43). In the midazolam group, 35% of the patients showed a decrease in oxygen saturation, whereas no adverse events happened in the opioid group.

**Remifentanil**

Remifentanil is a synthetic opioid with the analgesic potency of fentanyl, but an extremely short duration of action (begin 30-60 s, peak 2.5 min, termination half-life 8-10 min). Metabolism takes place by nonspecific esterases. This is useful especially in situations making a predictable termination of its effect necessary. Akcaboy et al. showed that remifentanil during colonoscopies – used as bolus injection combined with a low dose continuous infusion (0.05 µg/kg/min) and 2 mg midazolam - provides appropriate amnesia and sedation compared with propofol. Analgesia was even better with lower discomfort scores among patients. Drawback of remifentanil, however, was that it caused nausea and vomiting during the recovery phase and delayed patients’ discharge. Haemodynamic instability with a significant decrease in heart frequency, NIBP, and impaired oxygen saturation levels were additional disadvantages of remifentanil bolus injection. Nonetheless, gastroenterologists’ and patients’ satisfaction was higher and duration of colonoscopy was shorter compared with the propofol group. Probably the more conscious sedated patient cooperated more easily. Similar results were reported by Fanti et al. using remifentanil patient controlled analgesia (PCA) (0.5 µg/kg) in combination with midazolam.

Moerman et al. compared high-dose remifentanil (starting with 0.5 µg/kg as bolus injection with a continuous infusion of 0.2 µg/kg/min) with propofol (starting with 1 mg/kg as bolus injection with a continuous infusion of 10 mg/kg/h). Both combinations created a sufficient condition to perform colonoscopy. Emergence times and recovery of cognitive function were faster in the remifentanil group and haemodynamic disturbances were reduced compared to propofol. However, a significant problem in the remifentanil group was the respiratory depression rate. Patients in the propofol group were more satisfied than in the remifentanil group, probably because of the deeper sedation level caused by propofol. Greilich et al. compared remifentanil versus meperidine in older patients undergoing colonoscopy. Although overall satisfaction was the same in both groups, patients treated with remifentanil showed higher scores for anxiety and pain compared to the meperidine group.

In a recent study by Manolaraki, safety and efficacy of a standard sedation combination (midazolam and pethidine) during colonoscopy were compared with remifentanil (starting with a bolus of 1 µg/kg for 1 min combined with a continuous infusion of 0.05-0.2 µg/kg/min). Although mean levels of pain with remifentanil were higher than those with midazolam and pethidine, patients and endoscopists were likewise satisfied in both groups. Respiratory depression rate was significantly lower in the remifentanil group, most likely due to avoiding bolus injection of remifentanil and preferring careful titration. Importantly,
a much faster discharge of patients in the remifentanil group was observed. The necessity for continuous application and its negative side effects (nausea, vomiting and possible haemodynamic and respiratory complications) are serious limitations for routine use of remifentanil. Because only trained users (anaesthesiologists, anaesthesia nurses) would administer remifentanil, additional staffing costs will be associated with this analgesic regimen.

Alfentanil

Alfentanil is a µ-receptor opioid that has its maximal effects - comparable to remifentanil - within 1 to 2 minutes after injection and an elimination half-life of about 100 minutes. Metabolism takes place in the liver. Only 1% of alfentanil is found non-metabolised in the urine. Thus, in patients with liver dysfunction a more prolonged and pronounced effect can be expected. Dose-dependency allows for achieving different levels of awareness, cooperation, and psychomotor capacity more easily.

The only study addressing the use of alfentanil (10 µg/kg) for colonoscopies as a mono-drug was performed by Di Palma et al.\textsuperscript{27} The authors compared alfentanil with midazolam/alfentanil (n=11) and meperidine/midazolam (n=11). Patients receiving alfentanil (n=13) were less likely to require oxygen supplementation because of desaturation (8 versus 55% with alfentanil/midazolam and 27% with meperidine/midazolam), and suffered from less pain. There were no differences in haemodynamics (ECG, NIBP), recovery time, complication percentage, and patients’ discomfort. Therefore, Di Palma et al. came to the conclusion that alfentanil alone had no further advantage. However, the safety aspect – significant less desaturation episodes – makes the substance worth to be examined in more detail.

Usta et al.\textsuperscript{34} compared patient-controlled analgesia (PCA) with alfentanil (mean 1000 µg) versus fentanyl (mean 80 µg) for colonoscopies. Both opioids were given in combination with midazolam (group alfentanil: 2.34±0.96 mg, group fentanyl: 2.16±0.9 mg). Worth mentioning, analgesia was not completely patient-controlled. Patients received a loading dose of 500 µg alfentanil and were asked to request a further bolus (by pushing the button), when they felt pain. If sedation score exceeded 3 (OAA/S), further midazolam was added. Patients within both groups showed the same satisfaction score after colonoscopy and were disposed to undergo colonoscopy again. No adverse events (e.g. respiratory depression, haemodynamic changes) were observed. As expected, recovery was significantly shorter with the use of alfentanil compared to fentanyl. The author’s conclusion focussed on alfentanil, although midazolam was also administered as a sedative agent.

No other studies addressed the use of alfentanil for colonoscopies. In neurosurgical patients undergoing stereotactic brain biopsy, Bilgin et al.\textsuperscript{35} compared the effects of alfentanil, fentanyl, and remifentanil analgo-sedation combined with midazolam on haemodynamic and respiratory parameters. Alfentanil (10 µg/kg) initially led to a reduction in minute
volume and SpO₂, though without any clinically relevant respiratory depression. This effect was aggravated by additionally sedation using benzodiazepines.  

Nitrous oxide (N₂O)

Nitrous Oxide is a gas of low solubility that is rapidly absorbed (within 60 s) and eliminated unchanged via the lungs. Available in a fixed 50:50 combination with oxygen (Entonox®/Relivopan®/Livopan®), it is widely used in obstetrics and dentistry for more than 160 years. It is known for a rapid onset and termination of action and only minimal side effects. Its analgesic properties are attributed to inhibition of N-Methyl-D-aspartate (NMDA)–receptors; the anxiolytic and sedative properties are referred to activation of Gamma Amino Butyric Acid (GABA)-receptors. In animal studies, N₂O induced the release of opioid peptides in the brainstem followed by the activation of descending noradrenergic inhibitory pathways. Hence, N₂O modifies pain processing in the spinal cord and induces analgesia - without loss of consciousness.  

Welchman et al. performed a systematic review addressing sedation during colonoscopies, comparing N₂O to opiates – given intravenously – partially combined with midazolam. Unfortunately, only a small number of patients have been included, and among those a large diversity existed. In addition, no validated scores were used to assess patients’ satisfaction. The data showed that N₂O use on demand was not sufficient enough to adequately reduce pain, probably because a short lag time exists before analgesia is reached by N₂O. Løberg et al. could show that N₂O on demand is not really effective in the substitution of intravenous medication in patients undergoing colonoscopy. However, combining a start dosage of N₂O for 2 minutes administered by the patient himself on demand showed that N₂O was superior to analgo-sedation with midazolam combined with fentanyl concerning pain experiences, satisfaction, and compliance to undergo colonoscopy again. In contrast, Forbes et al. reported that Entonox® was less effective than meperidine/midazolam with respect to pain scores, but allowed for faster recovery. Prediction of painful manoeuvres during colonoscopy is difficult, and the patient might use N₂O too late to timely achieve an adequate pulmonary concentration necessary for subsequent pain reduction. Maslekar et al. compared continuous inhaled Entonox® with patient maintained target controlled infusion with propofol. They found no differences between N₂O and propofol regarding pain relief, sedation, and mobility of the patients.  

N₂O for short acting procedures is considered safe. Onody et al. analysed 35,828 questionnaires and demonstrated a rate of all adverse effects of 4.4%, from which 86% counted for gastrointestinal (nausea, vomiting) and neuropsychiatric (dizziness, headache, hallucinations) disorders. The only proven toxic effect of N₂O concerns interaction with vitamin B12, which also depends on duration (6 hours) and extent of exposure. Animal studies suggest a problem
associated with chronic exposure to $N_2O$, whereby the exact level to induce patient harm cannot be predicted. Only long-term exposure to $N_2O$ in sufficient concentrations seems to produce irreversible, toxic changes and has been associated with reproductive, haematologic, immunological, neurological, liver and kidney disorders. Hence, administration to patients for a short-term colonoscopy procedure seems to be safe. Attention should be paid for personnel working in environments in which $N_2O$ is used the whole day, especially without an adequate extraction system.

The safety level for $N_2O$ exposure is yet not clearly defined. The National Institute for Occupational Safety and Health recommended “an exposure limit for $N_2O$ of 25 parts per million (ppm) as a time-weighted average for a normal 8-hour workday and a 40-hour workweek.” The American Conference of Governmental Industrial Hygienists has assigned for $N_2O$ an exposure limit of 50 ppm. In Germany, the occupational exposure limit is 100 ppm. Lacking exact data, it is important to minimise exposure. Every $N_2O$ apparatus must have a scavenging system with sufficient extraction and routinely checked for leaks. A minimum air exchange of 2-3 per hour must be guaranteed, when $N_2O$ is used. Patients should wear an on demand valve mask perfectly fitting their faces and be suggested not to speak during colonoscopy. After finishing the procedure and stopping $N_2O$, patients should receive 100% oxygen for 3-5 minutes via the mask.

**CONCLUSION**

The discussion on the ideal analgesic agent for colonoscopy demonstrates that in fact none of the latter agents is ideal. Almost all have side effects, have less patient satisfaction scores, have been used with sedatives, or have been studied in very small trials. But if pain is relieved adequately during colonoscopy, sedation is indeed not required in a huge number of patients. The use of $N_2O$ instead of IV drugs is "no laughing matter", for several reasons: $N_2O$ with a loading dose and continuous administration provides adequate analgesia with a patient being awake and co-operative; after cessation patient is awake, ready to get the information necessary, and to leave the hospital soon after the procedure. Patients without escort and living alone may in particular benefit from the fast recovery of psychomotoric functions provided by $N_2O$. However, there are some limitations of $N_2O$ like uncertainty about chronic side effects and need for air conditioning and efficient ventilation together with efficient active scavenging systems.

Alfentanil is a strong analgesic, facilitating a fast turnover of satisfied, pain free patients, which are able to cooperate with the endoscopist. Its respiratory depressant effects are without clinical impact. Moreover, all actions of alfentanil can be immediately reversed by naloxone, making the substance safe in general use. Further studies are needed to assess efficiency and last but not least patients and physicians satisfaction level with use of these two forms of analgesia.
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