Sedation outside the operation room

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Citation for published version (APA):
Eberl, S. (2017). Sedation outside the operation room.
A RANDOMISED CONTROLLED MULTICENTRE TRIAL: THE SPEKA STUDY. SEDATION WITH PROPOFOL DURING ERCP: IS THE COMBINATION WITH ESKETAMINE MORE EFFECTIVE AND SAFER THAN WITH ALFENTANIL? A STUDY PROTOCOL

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Submitted Trials
\textbf{ABSTRACT}

\textit{Background:} Endoscopic retrograde cholangiopancreatography (ERCP) is a gastrointestinal procedure that requires a relatively motionless patient during the intervention. Deep sedation by intravenous propofol combined with an opioid has recently become the preferred sedation technique. The drawback of this technique can be serious cardiorespiratory depression. Esketamine has hypnotic, analgesic, and sympathomimetic effects. Our assumption is that a combination of propofol with esketamine reduces the dosage of individual drugs, thereby minimising sedation side effects while keeping the same satisfaction level of patients and endoscopists.

\textit{Methods/design:} The study will be performed as a randomised controlled multicentre trial. Patients undergoing ERCP, \( \geq 18 \) years, ASA classification I – III will be randomised after written informed consent to group K (propofol/esketamine) or to group A (propofol/alfentanil). Primary outcome, reflecting effectiveness of sedation, is the total dose of propofol. Secondary outcome parameters are patients’ and endoscopists’ satisfaction with the procedure and the number of sedation related cardiorespiratory events. Data - regarding sedation related incidents - are collected by recording of oxygen saturation (SpO\textsubscript{2}), respiratory rate (RR), end-tidal CO\textsubscript{2} (etCO\textsubscript{2}), heart rate (HR), arrhythmias (ECG), and non-invasive blood pressure (NIBP) measurements. Satisfaction parameters are collected by means of questionnaires before and after the procedure and on the following day.

\textit{Discussion:} Esketamine is known for its effective anaesthetic and analgesic effects maintaining spontaneous breathing and airway reflexes. Due to an increase in sympathetic tone, hypotension and cardiac depression is less common. Unfortunately, esketamine is also known for its psychotomimetic effects. We aim to demonstrate that the combination of esketamine with propofol for sedation in patients subjected to ERCP interventions is nevertheless superior to a combination of propofol with an opioid.
BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is a complex, often painful gastrointestinal procedure. It is used for both, diagnostic purposes in biliary and pancreatic diseases and also for therapeutically interventions such as sphincterotomy, gallstone extraction, and biliary and pancreatic duct stenting. Because any movement of the patient could importantly affect success of the ERCP, procedures are usually performed under deep sedation or even general anaesthesia with the patients in semiprone or prone position. Over the last decade the combination of propofol and an opioid has become the preferred sedative regime during ERCP in many countries, despite known side effects, such as hypotension and respiratory depression. Opioids, especially when used in combination with sedative-hypnotics, can not only aggravate clinically significant respiratory depression but also increase the incidence of postoperative nausea and vomiting.

Esketamine, the s-enantiomer of ketamine, is not only a well-known sedative but also has strong analgesic properties. Furthermore, its sympathomimetic qualities can counteract the haemodynamic depression of propofol and therefore reduce the risk of cardiovascular and respiratory depression during sedation. Esketamine could thus be a safer additive to propofol than opioids to achieve a sufficient depth of sedation with less negative cardiopulmonary side effects due to dosage reduction of propofol and omission of opioids. A potential problem concerning esketamine could be its psychotomimetic effects, such as visual disturbances, vertigo, or nausea that could compromise patient satisfaction. There is still little evidence for an improved safety profile of a combination of propofol/esketamine, and it is still open to discussion whether esketamine psychotomimetic effects play a significant role in outpatient treatment.

METHODS/DESIGN

Aim of the study

We hypothesise that procedural sedation with propofol and esketamine will reduce the number of sedation related side effects during ERCP with superiority to standard propofol/alfentanil sedation and thus demonstrate a higher safety and satisfaction profile as the former combination.

To test this hypothesis, we compare two groups. Group K receives propofol/esketamine sedation; group A gets propofol/alfentanil sedation during ERCP. Both groups receive standard deep sedation with propofol target controlled infusion (TCI) provided by specialised sedation anaesthesia nurses.
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**Trial design**

This trial is designed as a prospective randomised controlled multicentre study. It will be reported following the SPIRIT statement. Sponsor of this trial is the Department of Anaesthesiology of the Academic Medical Centre (AMC) in Amsterdam. The sponsor is responsible for the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

**Participants**

*Number of patients’ needed*

Primary objective is the total dosage of propofol. Sample size calculation is based on retrospectively obtained propofol data from previous ERCPs, collected in our hospital sedation database. The mean (± standard deviation) dosage of propofol during ERCP’s was 580±190 mg. Therefore, we will have to study 76 patients in each group, given a power of 0.80 and a type I error of 0.05 to reduce the amount of propofol by 15%. With a dropout rate of 10 % the estimated sample size will be 166 patients.

*Eligibility*

The study takes place at the Department of Gastroenterology and Hepatology in the Academic Medical Centre (AMC), Amsterdam and the Department of Gastroenterology and Hepatology in the Tjongerschans hospital, Heerenveen, the Netherlands, beginning December 2015 to January 2018. Eligible patients for participation in this clinical trial are those scheduled for elective ERCP under deep propofol sedation, ≥ 18 years, and with ASA physical state I-III, with written informed consent.

*Exclusion criteria*

Patient are excluded, if the following criteria in the patients’ anamnesis, are applicable:

- Age range < 18 years
- ASA IV and V
- Known allergy to planned medication
- History of unregulated or malignant hypertension
- Significant ischaemic heart disease
- History of psychological problems or psychiatric disease
- Use of drugs that affect the central nervous system
- Substance abuse
- Chronic pain
- Pregnancy
• Seizure disorders
• Increased intracranial pressure

The schedule of enrolment, intervention, and assessment is reported according to the SPIRIT statement.

Consent

Patients’ medical history and their current state of health are screened on paper during standard anaesthetic preassessment before the scheduled sedation. The investigator uses the anaesthetic preassessment form to screen patients for in- and exclusion criteria. Patients meeting inclusion criteria are contacted by phone to verify criteria and asked for their willingness to participate in this study. If they agree to participate, further information is send by mail. Final inclusion occurs after written informed consent at the day of the procedure.

If patients deny taking part in the study, they are sedated according to the AMC standards with propofol and alfentanil.

Randomisation

Patients are randomised online in both centres after signing informed consent using the ALEA software program provided by the Clinical Research Unit (CRU) of the AMC for centralised randomisation in clinical trial. Patients are allocated to a treatment arm after the anaesthetic nurse has entered patient details and absence of exclusion criteria in the ALEA program.

The study is performed as a single blinded study. Because of safety reasons the anaesthetic nurse is not be blinded to the treatment arm and will therefore perform the randomisation in the ALEA program. The patient, endoscopist, and investigator are blinded to the allocated treatment arm.

Patient data are collected on CRFs in each centre. Data processing will take place in the AMC using Castor database and will be performed by the investigator or study coordinator. The CRU also will monitor independently all side locations of the trial three times using duplicated measurements documented in the hospital data management systems with complete access to all databases.

Intervention

All patients are fasted at least 6 hours before ERCP. Antibiotic prophylaxis is given according to hospital standards. As a standard procedure, diclofenac 100 mg is administered rectally immediately before procedure to reduce post ERCP pancreatitis. Procedural sedation is performed by anaesthesia nurses trained in the standards of care for procedural sedation.
and analgesia (PSA) according to the Dutch national guidelines. An anaesthesiologist is available for liaison, supervision and emergency help.

Insufflation of the duodenum during ERCP is done with CO₂ to reduce periprocedural pain and abdominal distension in comparison to insufflation of air.

Patients are asked to complete a questionnaire before procedure to assess baseline pain levels, drowsiness, nausea, perception, and mood using a Visual Analog Scales (VAS) (0-100). Baseline assessments of the Modified Observer’s Assessment of Alertness/Sedation Scale (MOAA/S), the Aldrete recovery score and measurements of heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR), and oxygen saturation (SpO₂) are recorded.

After placement of an intravenous line, an infusion of 500ml NaCl 0.9% is started at the rate of 250 ml/h. Five minutes before insertion of the endoscope, glycopyrrolate 0.2 mg, and lidocaine 50 mg are given iv. Then patients are asked to place themselves into the prone or semiprone position. Two l/min of oxygen are administered by nasal cannula during ERCP, and HR, SpO₂, RR, ECG, NIBP, end-tidal carbon dioxide (etCO₂), and sedation level measured by the MOAA/S are collected at 5-minute intervals. An independent, blinded observer collects research data.

Both groups are sedated by a propofol Target Controlled Infusion (TCI) system (Propofol 1% MCT Fresenius). TCI means a weight pre-programmed system using a pharmacokinetic model to attain a specific estimated propofol plasma target level. We start propofol TCI in both groups with a targeted plasma level of 1.5 μg/ml.

Reaching this plasma level, group K is treated with esketamine (Ketanest S, Pfizer) 150 µg/kg, group A receives alfentanil (Rapifen, Janssen-Cilag) 2.0 µg/kg. After 2 minutes propofol TCI is stepped up – if needed - to a maximum-targeted plasma level of 2.5 µg/ml.

Before starting the endoscopic procedure, patients are assessed for their level of sedation using the MOAA/S scale yielding at a score of < 2. The modified form of the MOAA/S scale uses not only the responsiveness component of the original scale (awake (5) - unresponsive (1)) but is extended with assessment of painful stimuli. As reaction of painful stimuli are still possible at anaesthetic levels that block reactions to verbal commands, prodding, or shaking, they can be used to assess deeper sedation levels.

If MOAA/S is above 2, e.g. the patient does not sustain intervention, additional sedation is provided with TCI increments of 0.5 µg/ml in plasma target level. These very small steps are performed in order to avoid deep sedation. For every step up of propofol TCI additional esketamine 50 µg/kg or alfentanil 1 µg/kg is added. Maximum dosage is 500 µg/kg ketamine or 7.5 µg/kg alfentanil.

The total amount of all used medication (propofol, esketamine, alfentanil) as well as all time periods (total procedure time, time between end of the endoscopy till patient is ready for transport to the recovery unit) is noted.
At the recovery room, monitoring is limited to SpO\textsubscript{2}, RR, ECG, NIBP, and Aldrete score\textsuperscript{2} every 15 minutes. This score describes the patient’s motoric activity, mechanical respiratory function, oxygen saturation, blood pressure, and consciousness and is designed to assess patient recovery after sedation. The total score is 10. During the time in the recovery room, patients have to complete the identical questionnaire as they completed at baseline concerning pain, drowsiness, nausea, perception, and mood using VAS scales (0-100). Following daily standards, post-procedural pain is mentioned as VAS > 40 and is treated with 2 mg morphine intravenously, nausea with a VAS > 40 will be treated with 4 mg ondansetron intravenously. Patients have to stay for at least 1 hour in the recovery room. “Ready for discharge” is declared when an Aldrete Score ≥ 9 is met, and the patient is awake with stable vital signs, able to walk around, and without nausea or dizziness. On the next day, a follow-up telephone call will take place.

**Primary objective**

*Definition of primary objective*

Primary objective of this study - reflecting the effectiveness of coadministration of propofol and esketamine - is the total dose of propofol used during the procedure.

*Assessment of primary objective*

The total amount of propofol, esketamine, and alfentanil will be noted.

**Secondary objectives**

*Definition of secondary objectives*

Secondary endpoints focus on satisfaction of patients and endoscopist with sedation, the side effects of sedation, and on haemodynamic stability and safety - being reflected in the number of respiratory and cardiovascular events.

*Assessment of secondary objectives*

Pain, sedation level, and side effects as nausea and psychotomimetic effects are recorded on questionnaires that patients have to fill in before and after the procedure. To assess post-procedural satisfaction, patients are contacted the day after the procedure by telephone. In addition, endoscopists’ experiences with sedation are recorded on a questionnaire directly after the procedure.
Questionnaires

Before ERCP, after the procedure, at arrival on the recovery unit, and on the following day, patients are asked to complete questions concerning pain levels, drowsiness, nausea, perception, and mood using VAS scales (0-100). Pain intensity will be assessed by using a 100-mm VAS scale, with 0 = no pain and 100 = worst possible pain. Nausea will be measured by a VAS scale, with 0 = none and 100 = vomiting. Perceptual change will be assessed in five categories (i.e. body, surroundings, time, reality, colours, and sounds) by using a VAS scale anchored by “normal” at one end and “extremely” at the other end. Mood states are ranked between 0 and 100 in five categories: anxious/composed, hostile/agreeable, depressed/elated, tired/energetic, and confused/clearheaded (modified from Mortero et al. [8]).

The day after the procedure, patients are contacted by telephone to assess post procedural satisfaction. The same questions from part one and two of the patient questionnaire are asked to the patient. Patients are also interviewed about their total satisfaction with the procedure, about their physical activity level using a five-point rating scale: 1 = chair bound, 2 = minimal (i.e. can go to the bathroom), 3 = moderate (i.e. can go around the house and garden), 4 = almost normal, and 5 = normal, and if they would recommend this sedation regime to one of their friends.

Endoscopists have to fill in questionnaires concerning their estimation of pain, sedation, ease of performance, and satisfaction with the procedure.

Pulmonary and cardiovascular vital signs are electronically recorded throughout the procedure and include: SpO₂, measured by pulse oximetry, etCO₂, RR, HR, arrhythmias, and NIBP. Sedation related pulmonary and cardiovascular incidents were defined according to the International Sedation Task Force of the World Society of Intravenous Anaesthesia (SIVA) consensus statement for standardised definitions and terminology for sedation related adverse events [9]. Pulmonary incidents are defined as: Oxygen desaturation (SpO₂ 75–90%) for <60 s, severe (SpO₂ < 75% at any time) or prolonged (SpO₂ < 90% for > 60 s) oxygen desaturation, apnea, prolonged apnea (> 60 s), airway obstruction with need for airway interventions: facemask ventilation, guedel, nasopharyngeal airway, and endotracheal tube. Cardiovascular incidents are defined as: bradycardia*, tachycardia*, hypotension*, hypertension* (* as a change of > 25% from baseline and/or necessitating an intervention), cardiovascular collapse and arrest.

In addition, the use of atropine, ephedrine or phenylephrine intravenously to treat hypotension or bradycardia is noted.

Statistical analysis

Statistical analyses will be performed using SPSS statistics.

All data will be checked for normal distribution using the Kolmogorov test. For normal
distributed, continuous variables an independent Student’s t-test will be used, and the variables will be presented as mean ± standard deviation (SD). Not normally distributed data will be compared using the Mann-Whitney U-test where appropriate, and data will be presented by the median and interquartile range (IQR). For categorical variables, cross tabulation and the Pearson’s chi-squared test will be applied and variables will be allegorised as number and/or percentage of the total. To compare the continuous measurements of HR, NIPD, and SpO₂ between both groups, the area under the curve (AUC) for each value will be calculated over the different measurement time points during the procedure. A p-value< 0.05 will be considered statistically significant. Confidence intervals will be mentioned where appropriate.

**Ethical approval**

This trial is conducted in accordance with the protocol and in compliance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (1989) and Good Clinical Practice (GCP). It is registered in the Nederland’s Trial Register (NTR5486). Ethical approval was obtained from the Medical Ethics Committee of the Academic Medical Centre, Amsterdam, the Netherland (NL). The National Authority, the Central Committee on Research Involving Human Subjects (CCMO), performed a marginal review and there were no objections to perform this study (NL53999.018.15).

**DISCUSSION**

Propofol combined with an opioid replaces more and more benzodiazepines for sedation during ERCP. It is in the meantime the standard sedative agent due to a better titration of the different sedation levels, shorter recovery time, and more patient satisfaction. However, a serious drawback of propofol/opioid sedation is that sedation level can rapidly change from moderate to deep sedation, or even to general anaesthesia. Here, skilled airway support, which is not easy to perform in the prone position, may be required to prevent hypoxaemia. Cote et al. showed that in 12.8% (n=102) patients hypoxaemia occurred during propofol sedation, although propofol was administered by trained anaesthesia nurses. In 14.4% of the patients, tactile airway manoeuvres were necessary. Minimising respiratory risks is therefore important, to make sedation safer. A possible approach can be, to reduce the propofol dosage using the combination with other substances.

Previous studies used propofol combined with midazolam for ERCP sedation. This method significantly reduced the total amount of propofol required for sedation. Nevertheless, the synergistic sedation effects of both drugs increased the likelihood of respiratory depression and prolonged recovery time without any analgesic effect. Esketamine offers the advantages of minimising these side effects, making optimal use of the concept of synergy whilst being
an analgesic at the same time. Varadarajulu et al.\textsuperscript{13} demonstrated that the use of ketamine in difficult to sedate patients undergoing ERCP resulted in better quality and depth of sedation and analgesia. They observed shorter recovery times compared with opiate and benzodiazepine sedation. However, they concluded that it is necessary to conduct further randomised trials. Wehrmann et al.\textsuperscript{14} recommended the combination of propofol with ketamine because of its analgesic properties without cardiorespiratory depressant effects. Mortero et al.\textsuperscript{8} found that the combination of propofol and ketamine in small doses attenuates hypoventilation, produces positive mood effects without perceptual changes, and provides faster recovery of cognition in comparison to propofol alone during monitored anaesthesia. Ketamine is a favourable drug in haemodynamically instable patients. Despite its effective anaesthetic and analgesic effects, spontaneous breathing and airway reflexes are maintained and hypotension is less common due to an increase in sympathetic tone. Its s-enantiomer esketamine has been shown to be even more potent with an approximately 3-4 fold anaesthetic potency compared to racemic ketamine. The most common concerns about esketamine, however, are related to its mind-altering effects in cognition. It can produce psychotomimetic effects that may be associated with symptoms similar to dissociative states of mind.\textsuperscript{15} On the other hand, Nakao et al.\textsuperscript{16} showed that propofol used in clinical relevant dosages suppresses these effects via the activation of Gamma-Amino Butyric Acid (GABA) receptors. Unfortunately, there are only a few studies with only limited significance investigating the effectiveness of a propofol/esketamine regime with emphasis on the aforementioned safety aspects during ERCP and the eventually psychotomimetic effects such as visual disturbances, vertigo, or nausea that could compromise patient satisfaction and recovery after discharge home. The aim of our trial is to show that the synergy of esketamine and propofol can provide a better safety and satisfaction profile than the combination with an opioid during ERCP.
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