Sedation outside the operation room

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INTRODUCTION
AND OUTLINE OF THE THESIS
INTRODUCTION

The demand for monitored anaesthesia care (MAC) for diagnostic and therapeutic procedures outside the operating room (OR) increases continuously. A multitude of medical specialists, e.g. gastroenterologists, interventional cardiologists or radiologists, gynaecologists, dentists, and even psychiatrists ask for safe, but efficient anaesthesia support for more and more complex procedures. Today, also patients are more assertive and no longer willing to undergo painful or stressful situations without an adequate form of sedation or anaesthesia.

Therefore, anaesthesia departments have to recognise that it is necessary to move out of the OR comfort zone even if this means thinking outside the own box. It is known that procedures outside the OR have the potential to be more challenging than those performed in the OR: procedure settings and locations outside the OR very often do not have the standard of anaesthesia care that anaesthesia caregivers are accustomed to. In addition, the form of anaesthesia often varies from conscious to deep sedation or even general anaesthesia in patients often having a lot of comorbidities.

That means criteria that have to be considered for procedures under sedation outside the OR include a long list of variables that concern procedure, location, patient, and anaesthesia provider himself.

Hereby it is important to assess invasiveness, complexity and length of the procedure, the amount and severity of possible complications, and the level of sedation or analgesia needed to perform the procedure. It is also necessary to check anaesthesia requirements on location and post procedure recovery facilities carefully.

As the most important point, anaesthesia providers have to evaluate patient’s characteristics and comorbidities precisely as well as in form and content requirements on sedation providers themselves.

Given these requirements, a multidisciplinary cooperation of all key players in a hospital institution is necessary to determine the appropriate standards and hospital guidelines to provide optimal conditions for the procedure and the patient at affordable conditions. These standards should accordingly be evaluated based on their achieved outcomes in patient’s safety, the satisfaction of all parties - patient, anaesthesia provider and procedure operator - and the finally gained efficiency.

The new field of procedural sedation outside the OR belongs to the core functions of the anaesthesiologist, but besides the fact that this would be extremely cost intensive, there is a lack of manpower within the anaesthesia departments to meet the steadily increasing demand. Therefore, a discussion about the qualifications needed to provide safe and efficient sedation and the need for non-anaesthesiologists (non-physicians) taking over this task was pre-programmed.
The Ministry of Health, Welfare and Sport in the Netherlands adopted 2012 national guidelines on an assessment framework for sedation and analgesia outside the OR. Providers offering sedation outside the OR have to fulfil clearly defined structural requirements concerning sedation focusing on optimal procedural success and patient safety and comfort. One of the most important points was the introduction and legalisation of a structured education and training program for specialised non-physician sedation practitioners.

In cooperation with the University Medical Centre of Utrecht (UMCU), the Academic Medical Centre of Amsterdam (AMC) started for anaesthesia nurses a theoretical and on-the-job training program lasting one year. After successfully passing a final examination these specialised sedation practitioners work self-dependent under indirect supervision of an anaesthesiologist on the different locations outside the OR where they provide sedation ranging from mild over moderate to deep sedation levels, but no general anaesthesia.

It is important to know before reading this thesis that in the AMC the step - not only out of the OR - but also out of the circle of anaesthesiologists towards specialised sedation practitioners has been made already years ago. Today, both parties provide sedation outside the OR, but only anaesthesiologists give general anaesthesia.
OUTLINE OF THE THESIS

Part 1
The first part of this thesis focuses on the question which procedures might be suitable for sedation outside the OR, or whether these procedures should better be performed using alternative techniques as general or local anaesthesia.

In chapters 2 and 3, we focus on the transfemoral implantation of the aortic valve (TAVI). This procedure actually was started 2006 using general anaesthesia. Nowadays, an increasing number of implantations is performed under sedation or – as in the AMC - using only local analgesia.1,2,3,4

Chapter 2 is a critical editorial discussing the question: does the form of anaesthesia, which also means sedation, make the difference during TAVI procedures?5 Looking at the available evidence-based literature data, we cannot answer this question at this moment. Nevertheless, there are forceful arguments to avoid general anaesthesia and deep sedation during these procedures, preferring the fully awake patient only using local wound infiltration with local analgesics, but with a cardiac anaesthesiologist as member of the team.

Chapter 3 presents our own TAVI data:6 between April 2010 and May 2013, 178 patients underwent transfemoral TAVI under local anaesthesia combined with premedication or light sedation. Interventional cardiologists performed all procedures in a multidisciplinary team together with an anaesthesiologist in the cardiac catheterisation laboratory.

Chapter 4 attends to the different treatment options and the relevant form of anaesthesia - or sedation - for a rare, disabling gastroenterological disease: achalasia.7 Achalasia is characterised by a reduced motility of the oesophagus coupled with the inability of the lower oesophagus sphincter (LOS) to relax sufficiently. The outcome of this combination is stasis of food, liquid, and saliva above the LOS.8 Nowadays, there are different medical, endoscopic, and surgical possibilities to treat achalasia. All of these treatment options set as objective to reduce the spasm in the muscle layers of the LOS. Although the aim of the different therapeutic interventions is the same, all alternatives require a special anaesthesia approach.

Chapter 5 reviews the question: does each diagnostic or therapeutic procedure really need sedation?9 What is suitable if a procedure is only painful, but does not require a motionless patient? Is it analgesia, sedation, both, or nothing at all? And how to handle the special request for sedation demanded by the patient or operator?
As example for such a procedure we chose endoscopic colonoscopies. Colonoscopies are often associated with pain and fear. Dominitz et al.\textsuperscript{10} could show that 25\% of all people who never have had a colonoscopy before are willing to surrender median ninety days of their resting life to obviate this expected painful and scary procedure even if it is necessary. However, there are also patients where it is possible to perform a successful colonoscopy without any form of sedation.\textsuperscript{11,12,13} But even this latter group stated that there are moments during the procedure with enormous discomfort and painful episodes. Our review follows Moerman’s hypothesis: “If pain is the crucial point, why do we need sedation?”\textsuperscript{15} and we discuss the analgesic options to increase success-rates of a painful intervention without increasing risks due to sedation-induced adverse events.\textsuperscript{16,17}

**Part 2**

In part 2 of this thesis we discuss different drugs for analgo-sedation and their application during different procedures with special requirements concerning sedation.

The definition “sedation” is not unambiguous. It is a collective term for a drug-induced continuum ranging from consciousness to unconsciousness of the patient with all possible side effects like loss of airway patency or cardiovascular instability. Sedation levels range from minimal to moderate, to deep sedation, and finally to general anaesthesia.\textsuperscript{18} A clear understanding of this continuum is mandatory.\textsuperscript{19} During minimal sedation patients respond in a normal way to verbal commands. Cardiorespiratory functions are unaffected, whereas the cognitive function may be impaired. Moderate sedation is specified as further reduction of cognitive function. Patients could purposefully respond to verbal commands after light tactile stimulation. Spontaneous ventilation is completely sufficient. During deep sedation, cognitive function is further reduced, and patients cannot be easily awaked, but react on repeated or painful stimuli. Spontaneous ventilation can be insufficient. It may be necessary to assist patients to maintain airway patency. Cardiovascular functions are normally unimpaired. General anaesthesia means: patients are not arousable, even not after a painful stimulus. Assistance to maintain a patent airway and positive-pressure ventilation are often necessary. Analgo-sedation is a combination of analgesia and one of these above-mentioned sedation levels.

Therefore, it is important for each procedure to estimate, which component (analgesia and/or sedation) and also which level of sedation is really necessary and which could be passed. We should always consider, what is important for the respective procedure: is it the stress-free, the painless, the immobile, or the non-coughing patient?
Chapter 6 addresses the “analgesic - only” approach during CT colonography – a procedure which is due to the colonic insufflation comparable to colonoscopies regarding pain experience. We conducted a double blind placebo-controlled randomised multi-centre trial in ninety patients scheduled for elective CT colonography. After randomisation patients were allocated to get either placebo or alfentanil for pain therapy. Alfentanil is a µ-receptor agonist that has its maximal effects within 1 to 2 minutes after injection. It acts dose-dependent. This characteristic renders possible, to titrate alfentanil till the planned level of consciousness is reached. Primary objective was the difference in pain experience between both groups measured on an 11-point numeric rating scale (NRS). In this trial, alfentanil was applied under continuous monitoring of SpO₂, but without attendance of an anaesthesiologist or specialised sedation practitioner.

In Chapter 7 we again address the “analgesic – only” question. In a prospective randomised trial we investigated satisfaction of patients and endoscopists, and concurrent safety aspects of an “alfentanil - only” strategy compared to two other common forms of analgo-sedation in patients scheduled for colonoscopy. 180 patients were randomised in three groups: group A: alfentanil – solely an analgesic, group M: midazolam combined with fentanyl - a combination of analgesia and mild sedation, and group P: propofol combined with alfentanil – a combination of analgesia and deep sedation; in group A and M, analgo-sedatives were given by the attending endoscopy nurse and in group P by a specialised sedation practitioner. Cardiorespiratory parameters as ECG, heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SpO₂), and end-tidal carbon dioxide (etCO₂), and interventions were monitored. After procedure, endoscopists and patients completed questionnaires related to their experiences with endoscopy.

Chapters 8 and 9 address with dexmedetomidine a new substance for moderate procedural sedation. Dexmedetomidine is a short-acting selective alpha₂-adrenoceptor agonist with anxiolytic, hypnotic, and analgesic properties without respiratory side effects. This sounds like the ideal analgo-sedative for moderate sedation. Analgesic and anxiolytic effects combined with the properties of an ideal sedative (e.g. a fast begin and termination of action, the possibility to titrate to a planned sedation level, nevertheless a fast recovery, combined with an superior safety profile, and without the necessity for extra personnel). Propofol as the gold standard provides superior sedation with a fast begin and end of action. However, drawback of propofol sedation is the risk to progress from moderate to deep sedation or even general anaesthesia with impaired cardiorespiratory functions. Therefore, pharmacological agents like dexmedetomidine that have analgo-sedative effects without the risk of respiratory problems are of increasing interest.
Chapter 8 provides a description of pharmacodynamics, systemic effects, and possible applications of dexmedetomidine.\textsuperscript{24} In chapter 9 we compared in a randomised controlled study the satisfaction and safety of a group of patients receiving moderate sedation with dexmedetomidine with a second group sedated with propofol.\textsuperscript{25} Our study focussed on elective endoscopic oesophageal procedures for treatment of Barrett’s oesophagus. These procedures require patients who are sedated, but easily arousable to provide an excellent endoscopic view of the oesophagus. Thus, we tended to a level of sedation - using the observer’s assessment of alertness/sedation scale (OAA/S) - between 2 and 4, meaning that patients show maximal lethargic response to their name spoken in normal tone.\textsuperscript{26} Patients were constantly monitored for HR, SpO\textsubscript{2}, ECG, etCO\textsubscript{2}, NIBP, and non-invasive cardiac output (NICO). After the procedure, patients rated their satisfaction level using a validated questionnaire modified from the patient satisfaction with sedation instrument (PSSI).\textsuperscript{27} Endoscopists were asked about their experience using the corresponding clinician satisfaction with sedation instrument (CSSI) score.\textsuperscript{27}

Chapter 10 focuses on another promising drug for moderate sedation: remifentanil, an opioid with a rapid begin within 30-60 s, peak effect within 2.5 min, and half-life of 8-10 min. Remifentanil is metabolised by non-specific esterases resulting in a rapid systemic elimination. This is useful especially in situations making a predictable termination of its effect necessary. Lim et al. showed that remifentanil slowly titrated with a target controlled infusion (TCI) system successfully suppressed the coughing reflex during intubation.\textsuperscript{28} Intubation is a procedure that provokes irritation of the complete airway system in almost the same manner as bronchoscopy. Therefore, we used these findings to develop a concept for moderate sedation during bronchoscopy and bronchial thermoplasty (BT) consisting of remifentanil TCI combined with propofol TCI.\textsuperscript{29} BT is a novel bronchoscopic treatment for patients with moderate-to-severe asthma; it has been shown to improve quality of life and to reduce asthma symptoms and exacerbation rates.\textsuperscript{30} A complete BT treatment consists of 3 consecutive bronchoscopic procedures during which airways of the left lower lobe, right lower lobe, and finally both upper lobes are treated with radiofrequency.

We performed a prospective observational cohort study including 32 BT procedures in severe asthma patients. After each procedure, patients were requested to rate their overall satisfaction with sedation on a visual analogue scale (VAS). Similarly, bronchoscopists were asked to rate patients’ cooperation and tolerance. All sedation-related events and the number of performed radiofrequency activations on the airway were registered.
Chapter 11 focuses on esketamine - an old and at the same time new medicinal option for deep sedation. Esketamine is a well-known drug with extensive use in the prehospital environment and emergency and critical care departments over the last years. Our still on-going study investigates deep procedural sedation for endoscopic retrograde cholangiopancreatography (ERCP) - an endoscopic intervention that requires a relatively motionless patient to facilitate this difficult procedure. In the last years, deep sedation with propofol combined with an opioid has become the standard sedation approach. Unfortunately, drawback of this combination is often serious cardiorespiratory depression. Esketamine, the s-enantiomer of ketamine and also a non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist and opioid receptor agonist, 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 after ketamine application is less common. Patients are randomised to group K (propofol/esketamine) or to group A (propofol/alfentanil). Primary outcome is the dosage of propofol needed for adequate sedation. Patients` and endoscopists` experiences are measured by means of questionnaires before and after the procedure and on the following day. Haemodynamic and respiratory parameters, and incidents are recorded as surrogate parameters for patient safety.

We aim to demonstrate in this randomised controlled multicentre trial 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.

In daily practice, moderate and deep sedation is usually realised by drug therapy. But there are other non-medicinal options like acupuncture that can provide or support sedation measures.

Chapter 12 focuses on acupuncture, which has been used since a long time for multiple indications. Well known is the role of acupuncture in pain treatment. However, only few studies are published with respect to its use during sedation for endoscopic gastrointestinal interventions.

We hypothesised in this study that “verum” acupuncture causes not only analgesia, but also has a sedative effect that will allow to reduce the total dosage of propofol necessary for an adequate sedation level during colonoscopies. For this trial, 153 patients were after randomisation allocated to receive electro-acupuncture (EA), sham-acupuncture (SA), or placebo-acupuncture (PA) combined with deep sedation performed with propofol and alfentanil. In the EA group, patients received verum-acupuncture needles unilateral on three points. We chose points, which are relevant for sedation and for abdominal distension: Pericardium 6 (P6), Stomach 36 (ST36), and Large Intestine 4 (LI4). Group SA got sham-
acupuncture with acupuncture needles. Sham acupuncture thereby means that verum-acupuncture needles were placed 1 cm lateral and distal to the acupuncture points used in the EA group. Group PA received sham-acupuncture with placebo-needles (Streitberger needles) on the points also used in the SA group to exclude an effect of acupressure on the classic acupuncture points. Primary endpoint was defined as the total dosage of propofol. As secondary objective we determined satisfaction of patients and endoscopists measured by questionnaires.

Part 3
In this part of the thesis we focus on adverse events related to procedural sedation outside the OR. The overall number of sedation related incidents is relatively low, but their impact can be enormously since adverse events ascribed to moderate and deep sedation levels are frequently affiliated with the cardiorespiratory system. It is known that cardiorespiratory complications account for the greatest part of sedation-related morbidity and mortality.

Chapter 13 discusses the case of an anaphylactic shock during percutaneous evacuation of an echinococcus cyst. This procedure is usually performed under deep sedation outside the OR with a multidisciplinary team consisting of a sedation specialist, a radiologist, and a radiology technician. Every team member has his own expert field, but they are most often not trained to work as a team in a critical situation. An anaphylactic shock is such a critical situation. Although anaphylactic reactions during this procedure are rare (1.7%), they carry a mortality rate of 0.03% and ask for fast resolutions. We want to show with this case report that cognitive aids can help to solve this problem.

The final chapter 14 presents our own data from a nationwide prospective registration of complications during various procedure types with deep sedation performed by anaesthesia nurse practitioners in 24 Dutch hospitals from the 1st February 2015 to 1st March 2016. Hospitals were both, academic and district general hospitals. For this registry, we translated and modified the adverse event reporting tool from the International Sedation Task Force of the World Society of Intravenous Anaesthesia. We provided anaesthesia nurse practitioners with the possibility to fill in a paper copy of the tool or an electronic online version. We also collected patient age, ASA physical classification, medical history, method of preassessment, type of procedure, National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification of the procedure, attendance of an anaesthesiologist, and drugs used.
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