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1. ABSTRACT

Endoscopic retrograde cholangiopancreatography (ERCP) is a relatively common procedure utilizing fluoroscopy in the imaging of bile and pancreatic ducts and is used for diagnostic and therapeutic purposes. ERCP usually requires moderate to deep sedation to be successful due to considerable discomfort and pain for the patient. During the last two decades propofol, has become the sedative drug of choice for ERCP. There are several ways to administer propofol sedation. Traditionally, the anesthesiologist administers propofol, but today there are other ways to organize the procedural sedation, such as patient controlled sedation (PCS) and patient-maintained sedation (PMS). All these techniques have their advantages and disadvantages and no method has been found to be superior to others.

Assessment and recording the level of sedation during endoscopic procedures is advocated for in guidelines for sedation. There is currently no consensus on which method of assessment should be used.

Doxapram is a respiratory stimulant with both peripheral and central effects. Since respiratory depression is a common adverse effect caused by propofol sedation, the role of doxapram in ameliorating this depression is worth exploring.

Routine preoperative laboratory testing (RPLT) has been increasingly been questioned and several guidelines are advising against RPLT for surgery and endoscopy in general, but studies regarding ERCP and RPLT are lacking.

Four studies were performed in the gastrointestinal endoscopy unit of Helsinki University Hospital. First study (Study I) was a prospective study to investigate how PCS is adopted in clinical practice for ERCP and differences in outcomes using different sedation methods commonly in use. It included all patients with ERCP performed during a one-year period. The analysis of 1196 ERCPs on 956 patients revealed that patients using PCS consumed less propofol with a similar incidence of adverse effects when compared to the other methods.

Second study (Study II) was performed to evaluate different methods of assessment of sedation used in scientific literature for ERCP sedation, Bispectral index (BiS),
Richmond Agitation/Sedation Scale (RASS), a modified Ramsay Sedation Scale (mRSS) and modified Observer Assessment of Alertness and Sedation (mOAAS) in 200 patients with all scales simultaneously used. All scales were found to be reliable in assessing the level of sedation when compared to each other. However, in the clinical setting of ERCP sedation BiS may be preferable to the other methods because it does not require communication with the sedated patient.

The purpose of the third study (Study III) was to find out if RPLT was useful in predicting adverse effects caused by ERCP or sedation in the patient cohort of Study I. RPLT included basic blood count, creatinine, potassium, sodium, amylase and International Normalized Ratio/thromboplastin time. Multivariate analysis showed no association with RPLTs and post-ERCP pancreatitis. The rate of other adverse effects related to ERCP was too low for statistical analysis. Respiratory depression caused by sedation was not associated with abnormal RPLTs. Cardiovascular depression caused by sedation was found to be related to thrombocytopenia and in male patients, hyponatremia. The clinical significance of the relation to cardiovascular depression remains unclear and is probably related to other health issues.

The fourth study (Study IV) investigated the use of doxapram as an adjunct to BiS-guided deep propofol sedation in order to reduce respiratory apneic episodes and hypoxemia. Fifty-six patients were randomized to receive either doxapram or placebo in 1:1 ratio in a prospective double-blinded protocol and resulted with no statistically significant differences between the groups.

In conclusion, no superior method for sedation or for the assessment of sedation for ERCP could be identified, but PCS and BiS remain the most clinically desirable protocols. The results suggest that the practice of RPLT should be abandoned and an individual preoperative laboratory testing should be adopted. Doxapram seems ineffective in preventing respiratory depression caused by propofol sedation.
2. LIST OF ORIGINAL PUBLICATIONS


II Jokelainen, Jarno; Mustonen, Harri; Kylänpää, Leena; Udd, Marianne; Lindström, Outi; Pöyhiä, Reino: Assessment of sedation level for endoscopic retrograde cholangiopancreatography - a prospective validation study. Scandinavian Journal of Gastroenterology, 2018, 53, 3, 370-375

III Jokelainen, Jarno; Ismail, Shamel; Kylänpää, Leena.; Udd, Marianne; Mustonen, Harri; Lindström, Outi; Pöyhiä, Reino: Effect And Predictive Value Of Routine Preoperative Laboratory Testing For Endoscopic Retrograde Cholangiopancreatography. Scandinavian Journal of Surgery, 2019, 1457496918822616

IV Jokelainen, Jarno; Belozerskikh, Anna; Mustonen, Harri; Udd, Marianne; Kylänpää, Leena; Lindstöm, Outi; Mazanikov, Maxim; Pöyhiä, Reino: Randomized clinical trial: Doxapram as an additive to propofol sedation for endoscopic retrograde cholangiopancreatography - a placebo-controlled, randomized, double-blinded study. Surgical Endoscopy, 2020,
3. ABBREVIATIONS

AAS – Anesthesiologist administered sedation

ASA – American Society of Anesthesiologists

BiS - Bispectral index

EEG – electroencephalography

ERCP - endoscopic retrograde cholangiopancreatography

ESA – European Society of Anesthesiology

ESGE - European Society of Gastrointestinal Endoscopy

ESGENA - European Society of Gastroenterology and Endoscopy Nurses and Associates

EtCO₂ - end tidal carbon dioxide

HFNO - High flow nasal oxygenation

IQR - interquartile range

mOAAS - modified Observer Assessment of Alertness and Sedation

mRSS – modified Ramsay scale

PCS – patient-controlled sedation

PMS - patient-maintained sedation

PSA - procedural sedation and analgesia

PK – Prediction probability

PSC - primary sclerosing cholangitis
RASS - Richmond Agitation/Sedation

RPLT - routine preoperative laboratory testing

SE – standard error

SpO2 - peripheral oxygen saturation

TASK - TWIK-related Acid Sensitive K channel

TCI – target-controlled infusion
4. INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a very demanding endoscopic procedure that gives valuable information about the structure and pathology of the biliary and pancreatic ducts and can be used to take biopsies and treat obstructed ducts. ERCP was first described in 1968(1) as a diagnostic tool for visualizing the duodenal papilla and the pancreatic duct. Since then it has been demonstrated to be effective in diagnosing and treating several disorders, such as choledocholithiasis, biliary tract obstruction caused by biliary, pancreatic and other malignancies, complications of chronic pancreatitis including pancreatic duct stenosis and pseudocysts, primary sclerosing cholangitis (PSC), and postoperative biliary or pancreatic duct complications. It is estimated, that the need for ERCP is about 50-100 per 100 000 persons every year and the need will rise as novel techniques are developed(2, 3).

The procedure begins by inserting a duodenoscope into the duodenum via the mouth, esophagus and stomach. Air or now more commonly carbon dioxide is insufflated into the stomach and duodenum to enable visualization of important anatomical structures and enable the cannulation of the common bile duct or the pancreatic duct through the duodenal papilla. To aid cannulation glucagon or hyoscine butylbromide is often administered to reduce intestinal motility. After the cannulation fluoroscopy and contrast media is used to visualize either the biliary tree or the pancreatic duct, or both depending on the patient. Sphincterotomy using electrocoagulation is often required if the patient requires a stent placement of removal of biliary or pancreatic stones. Dilation and stent placement in the biliary or pancreatic ducts by hydrostatic wire-guided balloon may be needed if strictures of the ducts are encountered. The duration of the procedure varies considerably and is usually between 10 to 120 minutes depending on the type of procedure and the skill and experience of the endoscopist. Difficulty of ERCP is usually assessed by using the Schutz scale (4). However, this scale does have its limitations. For example, a grade I procedure may be a lot more challenging than a grade III procedure, but the grading is determined by the average difficulty of ERCP.
A patient experiences mild discomfort, nausea or even severe pain during ERCP especially if the ducts need to be dilated. Sedation is usually required to ease patient’s experience and to enable the endoscopist to perform the procedure and avoid complications. Monitoring during ERCP is often challenging due to prone positioning of the patient and the dim lighting of the endoscopy theater. There is not a consensus on the optimal method of sedation for ERCP and the approaches vary from minimal sedation by intravenous opioids and midazolam sedation to general anesthesia(5-7).

ERCP carries potential risks of complications in addition to its usefulness. The reported overall rate of complications for ERCP is around 10% but varies a lot depending on the study population and type of procedures (8, 9). Mortality rate varies similarly and is between 0.2-0.5%(8). The most common complications of ERCP are pancreatitis, bleeding, duodenal perforation, cholangitis and cardiopulmonary complications. Other possible complications include portal venous air or carbon dioxide embolism caused by gas insufflation during the procedure, cholecystitis, stent migration, pneumothorax or pneumomediastinum, liver abscess and ileus. In order to avoid complications standard preoperative testing and pharmacological interventions have been used(10). The value of routine testing has been questioned over the past years (11, 12).

In order to make ERCP bearable and safe for the patient, the present study evaluates the sedation protocol (I-II), pharmacological intervention of respiratory depression caused by sedation (IV) and the value of routine testing before ERCP (III).
5. REVIEW OF LITERATURE

5.1. Procedural sedation

5.1.1. Monitored anesthesia care and procedural sedation and analgesia

American Society of Anesthesiologists (ASA)(13) and European Society of Anesthesiology (ESA)(14) have both released guidelines for procedural sedation.

The terms monitored anesthesia care or procedural sedation and analgesia are used by ASA and ESA respectively. ASA distinguishes monitored anesthesia care from moderate sedation in which sedation is administered by the doctor performing the procedure. Monitored anesthesia care is defined as a dedicated anesthesia professional administering the sedation and analgesia and includes deep sedation and even the potential for conversion to general anesthesia when needed. According to ESA “Procedural sedation and analgesia involves the use of hypnotic and/or analgesic medications to enable effective performance of diagnostic or therapeutic procedures effectively, whilst the patient is closely monitored for potential adverse effects.”

There is some controversy whether propofol sedation should be restricted to use by anesthesiologists or should non-anesthesiologists be allowed to administer sedation by propofol. European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) have published a guideline (15) for non-anesthesiologist administration of propofol for gastrointestinal endoscopy, but most national societies of anesthesiologists have not endorsed this practice. There is some evidence that this practice is safe at least in limited patient groups(16-20). It is also worth noting, that the use of propofol is limited to trained anesthesia and intensive care personnel in many countries, including Finland.
5.1.2. Assessing the level of sedation

There are several different methods for assessing the level of sedation and there is no international consensus on which method to use. The guideline by ASA uses a four-level scale shown in Table 1.

Table 1. Continuum of Depth of Sedation, Definition of General Anesthesia, and Levels of Sedation/Analgesia

<table>
<thead>
<tr>
<th>Functions</th>
<th>Minimal sedation (anxiolysis)</th>
<th>Moderate sedation/analgesia (conscious sedation)</th>
<th>Deep sedation/analgesia</th>
<th>General Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsiveness</td>
<td>normal response to verbal stimulation</td>
<td>purposeful response to verbal or tactile stimulation</td>
<td>purposeful response after repeated or painful stimulation</td>
<td>unarousable, even with painful stimulus</td>
</tr>
<tr>
<td>Airway</td>
<td>unaffected</td>
<td>no intervention required</td>
<td>intervention may be required</td>
<td>intervention often required</td>
</tr>
<tr>
<td>Spontaneous ventilation</td>
<td>unaffected</td>
<td>adequate</td>
<td>may be inadequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td>Cardiovascular function</td>
<td>unaffected</td>
<td>usually maintained</td>
<td>usually maintained</td>
<td>may be impaired</td>
</tr>
</tbody>
</table>
ESA employs a modified five-level Ramsay sedation scale(14, 21) shown in Table 2

**Table 2. Modified Ramsay scale**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully awake</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy</td>
</tr>
<tr>
<td>3</td>
<td>Apparently asleep but rousable by normal sleep</td>
</tr>
<tr>
<td>4</td>
<td>Apparently asleep but responding to standardized physical stimuli (e.g. glabellar tap)</td>
</tr>
<tr>
<td>5</td>
<td>Asleep but not responding to strong physical stimuli (comatose)</td>
</tr>
</tbody>
</table>

While not identical, there is a considerable overlap between the two scales, and both are useful when assessing the level of procedural sedation(22, 23). As indicated by the ASA scale, there is a growing need for interventions by the anesthesia provider as the level of sedation gets deeper. This puts an additional challenge to sedating patients for ERCP as the response of the patients to the drugs given and the nociceptive stimuli caused by the procedure are varied both individually and according to the stage of the procedure. There are also other means for assessing the level of sedation during procedural sedation. Typically, these are adopted from intensive care setting, such as Richmond Agitation/Sedation Scale (RASS)(24) shown in Table 3 and modified Observer Assessment of Alertness and Sedation (mOAAS)(25, 26) shown in Table 4.
Table 3. Richmond Agitation/Sedation Scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>Unarousable, no response to voice, physical stimulation or pain</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation, responds only to pain (such as bile duct dilatation)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation, responds to physical stimulation (such as shaking, manipulation of the gastroscope)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation, responds to repeated loud voice, eyes open &lt;10 seconds</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy, not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (&gt;10 seconds)</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>1</td>
<td>Restless, anxious but movements not aggressive, vigorous</td>
</tr>
<tr>
<td>2</td>
<td>Agitated, frequent non-purposeful movement, fights the procedure</td>
</tr>
<tr>
<td>3</td>
<td>Very agitated, pulls or removes catheters; aggressive</td>
</tr>
<tr>
<td>4</td>
<td>Combative, violent, immediate danger to staff</td>
</tr>
</tbody>
</table>

Table 4. Modified Observer’s Assessment of Alertness and Sedation

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No response to painful stimulus</td>
</tr>
<tr>
<td>2</td>
<td>Responds to painful stimulus only</td>
</tr>
<tr>
<td>3</td>
<td>Responds to loud speech</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to speech</td>
</tr>
<tr>
<td>5</td>
<td>Awake, responds to speech readily</td>
</tr>
</tbody>
</table>

Other methods for assessing the level of sedation are taken from monitoring of general anesthesia using processed electroencephalography (EEG), such as Bispectral index (BiS). BiS can be used for assessment of sedation level using all hypnotics except Ketamine(27) There have been several studies examining the use of BiS in sedation for endoscopy with varying results(28-31) and a recent meta-analysis and systematic review by Park et al. (29) found that the use of BiS did reduce the total consumption of propofol but did not have an effect on recovery times or adverse effects. BiS gives a numerical value of 0-100 based on EEG. There is no definite number to aim for when using BiS-guided sedation for ERCP, but BiS level of around 80 is generally considered sufficient for endoscopy(27) Other methods employing
EEG include Spectral entropy and qCON(32), however, these methods have not been as extensively studied in sedation of endoscopic procedures as BiS.

5.1.3. Sedative and analgesic medication

Gastrointestinal endoscopies are usually performed with minimal sedation using small amounts of benzodiazepines and opioids administered by the endoscopist along the lines suggested by the ASA guideline. Typical drugs used are benzodiazepines, such as midazolam, diazepam and opioids, like meperidine and fentanyl. However, propofol sedation has increased in popularity(33-36) during recent years following the EGSE guidelines. Several meta-analyses and review articles have been published on sedation for ERCP(5, 37-40), but there is no consensus on ideal sedative medication.

Propofol is a short-acting hypnotic agent that is widely used in anesthesia and sedation. It has no analgesic effect, so addition of analgesics is usually indicated in procedural sedation. A world-wide survey on endoscopist administered propofol sedation showed that propofol sedation seems to be very safe, with mortality of 1 in 161515 cases(19, 37) in general endoscopy population and a lot safer than administration of benzodiazepines and opioids(37, 41) with mortality rate of 11 in 100000. A Cochrane review by Garewal et al. found that patients receiving propofol sedation had shorter recovery times with no differences in adverse effects when compared to patients receiving benzodiazepines and opioids for ERCP(5). Patient satisfaction appears to be good and similar to midazolam sedation(42, 43).

Dexmedetomidine, an α₂-agonist, that is registered for sedation in the intensive care setting has recently been given an indication for intravenous procedural sedation by European Medicines Agency and it has been studied as a sedative for gastrointestinal endoscopy(44-46). According to studies it would seem to be better than midazolam but not superior to propofol in this setting. A study by Mazanikov et al. found that an adjuvant dexmedetomidine infusion was detrimental to successful sedation for ERCP by propofol-alfentanil PCS at least in alcoholics(47). An interesting off-label use of dexmedetomidine is intranasal dosing. Intranasally dexmedetomidine can be administered as premedication about 40 minutes prior to the procedure which
reduces consumption of other sedatives(48). As dexmedetomidine is a relatively recent addition to sedatives, more research on its use in endoscopic sedation is warranted.

Ketamine is an N-Methyl-D-Aspartate receptor antagonist that causes an atypical dissociative anesthesia and is used for sedation, anesthesia and analgesia. In gastrointestinal endoscopy it is mainly used with pediatric patients(49-52). It can be successfully used due to its unique pharmacodynamic profile in patients with unstable hemodynamics or whose respiration is easily compromised(53). Ketamine reduces consumption of midazolam when sedating high risk patients (54, 55) and gag reflex in sub-anesthetic doses(56).

Etomidate is a GABA\textsubscript{A} receptor modulator that has been clinically used in Europe since 1972. It has a very safe cardiovascular and respiratory risk profile. It also has a suppressive effect on the adrenal cortex, which may cause concern in critically ill patients. There are two randomized controlled trials investigating sedation with etomidate for ERCP(57, 58) and one randomized study for advanced endoscopic procedures including ERCP(59). In all these studies etomidate was found to be at least as safe as propofol in terms of cardiopulmonary adverse effects. Patient satisfaction seems comparable to propofol sedation(57, 59).

Table 5 presents randomized controlled trials that studied sedation with midazolam, propofol and dexmedetomidine for ERCP (43, 60-71).
<table>
<thead>
<tr>
<th>reference</th>
<th>sedative agent</th>
<th>results</th>
<th>number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2017</td>
<td>M vs. Propofol</td>
<td>No differences</td>
<td>100</td>
</tr>
<tr>
<td>Kongkam, 2008</td>
<td>Propofol vs. M+pethidine</td>
<td>Better recovery profile with Propofol</td>
<td>134</td>
</tr>
<tr>
<td>Krugliak, 2000</td>
<td>Propofol vs. M</td>
<td>Faster recovery and lesser hemodynamic instability with Propofol</td>
<td>32</td>
</tr>
<tr>
<td>Jung, 2000</td>
<td>Propofol vs. M</td>
<td>Faster recovery with Propofol</td>
<td>80</td>
</tr>
<tr>
<td>Wehrmann, 1999</td>
<td>Propofol vs. M+pentazocine</td>
<td>Propofol more effective, faster recovery</td>
<td>198</td>
</tr>
<tr>
<td>Riphaus, 2005</td>
<td>Propofol vs. M+pethidine</td>
<td>Better co-operation, faster recovery, less respiratory depression during recovery with propofol</td>
<td>150</td>
</tr>
<tr>
<td>Lu, 2018</td>
<td>M+remifentanil vs. Dex+remifentanil</td>
<td>less respiratory depression and higher patient satisfaction with Dex</td>
<td>198</td>
</tr>
<tr>
<td>Vargo, 2002</td>
<td>Propofol vs. M+pethidine</td>
<td>Faster recovery and better patient and endoscopist satisfaction with Propofol</td>
<td>75</td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>Propofol+M vs. M</td>
<td>better health care provider satisfaction and patient co-operation with Propofol</td>
<td>222</td>
</tr>
<tr>
<td>Kilic, 2011</td>
<td>M vs. Dex</td>
<td>higher endoscopist satisfaction with Dex</td>
<td>50</td>
</tr>
<tr>
<td>Goyal, 2016</td>
<td>Dex+ketamine vs. Propofol+fentanyl</td>
<td>Less hypotension, bradycardia and hypoxemia but longer recovery with Dex</td>
<td>83</td>
</tr>
</tbody>
</table>
Muller, 2008  Propofol+fentanyl vs. Dex  Shorter recovery and less hemodynamic instability with Propofol  26

Kim, 2014  Propofol+M vs. M  Faster sedation and recovery and higher patient co-operation with propofol  94

M=Midazolam, Dex=Dexmedetomidine

5.1.4. Patient-controlled sedation

Patient-controlled sedation (PCS) was first described in 1991 by Rudkin et al(72). PCS is a technique in which patients can self-administer sedative medication according to their individual needs during a procedure or for example mechanical ventilation in the intensive care unit(73). There are two main methods of PCS. In the first method an infusion pump administers preprogrammed boluses of the chosen sedative medication as requested by the patient via the use of a hand-held device connected to the infusion pump. It is also possible to have a background infusion and a lockout time when using PCS. The second method, often called patient-maintained sedation (PMS), employs a target controlled infusion (TCI) pump with a timer, which lowers the level of sedation over time unless the patient requests a deeper level of sedation by a hand held device attached to the TCI pump, which then increases the infusion speed of the sedative. A recent meta-analysis (74) found that PCS with propofol had no impact on the risk of oxygen desaturation, but the risk of rescue interventions for adverse effects was lower when using PCS when compared to clinician administered propofol sedation. However, the authors of the article remarked, that the quality of the data was relatively low. Another meta-analysis of PCS for colonoscopy(75) found that PCS was as feasible and effective as traditional intravenous sedation for colonoscopy and there was a trend towards faster recovery and less oxygen desaturation and hypotension. Several studies evaluating PCS for ERCP(76-79) have been performed. PCS using propofol with different additives, such as alfentanil and remifentanil, has been found to be superior to traditional sedation using midazolam and at least non-inferior to anesthesiologist administered propofol for sedation of ERCP patients.
5.1.5. General Anesthesia

Data concerning general anesthesia for ERCP is scarce. While conscious sedation of varying depth is generally the method of choice for ERCP, general anesthesia is also an option that some centers use regularly. Usual indications for general anesthesia are related to compliance issues, adverse effects to sedatives, and issues related to protecting from aspiration of gastric contents, airway problems or cardiovascular harm(80, 81). There is also some evidence, that general anesthesia may be associated with fewer adverse effects than sedation(82). A laryngeal mask airway is also a possibility during ERCP(83) and may offer a sort of middle ground between balanced general anesthesia and deep sedation, but data is lacking in this regard. A recent review article by Goudra et al. concluded, that general anesthesia and endotracheal intubation are not required for ERCP, but close monitoring, experienced anesthesia staff and the possibility of airway management are paramount(84).

5.1.6. Adverse effects

There are several potential adverse effects related to procedural sedation(14, 85). The most important adverse effect is arguably hypoxemia. Hypoxemia can be caused by the depression of the respiratory drive caused by sedative medication and opioids as the level of sedation deepens. Airway obstruction is also possible, caused by the relaxation of the tongue and pharynx due to excessive sedation. These adverse effects can be counteracted by naloxone and flumazenil, when caused by opioids and benzodiazepines(86). Respiratory support is usually indicated starting from supplemental oxygen up to and including endotracheal intubation and mechanical ventilation. Aspiration of gastric contents is also a threat, especially when the gastrointestinal tract is obstructed, there is gastroparesis or gastric bleeding. Administering sedation under such conditions is challenging.
Hypotension is about as common adverse effect as hypoxemia in sedation for endoscopy in general (87) and ERCP (57, 88). Generally systolic blood pressure of 90mmHg is considered sufficient for organ perfusion when lying down. Hypotension is usually attributed to sedatives or a vasovagal reaction. Both benzodiazepines and propofol can cause cardiovascular depression and hypotension, especially in conjunction with opioids. Hypotension in procedural sedation is usually corrected using standard treatments like correcting hypovolemia and vasoactive medications, such as ephedrine or phenylephrine. Myocardial ischemia and infarction are rare adverse effects related to sedation during endoscopy, but they may also present within a few days following the procedure. Sedation can predispose to myocardial ischemia via either hypoxemia or reduced myocardial perfusion, both of which can be attributed to sedation. Cardiac arrest can also occur, either due to myocardial infarction or other causes, such as air embolism caused by the endoscopy (89, 90).

5.2. Preoperative laboratory tests

Routine preoperative laboratory testing (RPLT) has been usual practice for a long time. The goal of RPLT is to detect abnormalities that may cause problems related to treatment chosen for a patient. This practice has been increasingly questioned lately on virtually all fields of surgery (91-98). The abnormalities found in RPLT seldomly affect the procedure (99, 100). There is a dearth of literature regarding the use of RPLT for endoscopic procedures, but a position statement by AGSE (101) declares that RPLT is not cost effective and may unnecessarily delay endoscopy and subject the patient to additional risks. Preoperative laboratory testing should be performed based on clinical judgement in an individual case-to case basis. However, RPLT is still deeply rooted in clinical practice of high-volume group of ERCP patients.
5.3. Doxapram

Doxapram was first synthesized in 1962(102) and is an analeptic drug and a respiratory stimulant. Both of these effects were initially thought to occur via stimulation of the central nervous system. The respiratory stimulant effect has later found to be mediated also by the stimulation of aortic and carotid chemoreceptors, specifically TASK-1 and TASK-3 (TWIK-related Acid Sensitive K channel). It is currently unclear, whether the central or peripheral effect is more important in mediating the respiratory stimulant effect.

In clinical practice doxapram has been used as a stimulant in respiratory failure related to chronic obstructive pulmonary disease(103) and sleep apnea(104). However, the effect of doxapram in these indications is not very substantial and other newer interventions, such as non-invasive ventilation, are more effective. In the perioperative setting doxapram has been used to facilitate faster recovery from general anesthesia because of its analeptic and respiratory stimulant properties. It was mostly studied in this setting in the 1960’s and 1970’s (105-108). With the advent of newer, faster acting anesthetics the need for analeptic drugs and respiratory stimulants has declined. There have been some newer studies done on doxapram with general anesthesia(109-111). These studies confirm the older findings that doxapram shortens recovery time after general anesthesia, even with modern anesthetics. The clinical significance of the shorter recovery time is negligible, on average 2-5 minutes faster recovery. The use of doxapram as a method of preventing respiratory depression during sedation and anesthesia has not been investigated. Like all drugs, doxapram does have some side effects(102), such as cough, dyspnea, tachypnea, headache and dizziness. Doxapram has also been associated with agitation in the intensive care setting(112). Doxapram is contraindicated in patients with obstructed airway and other mechanical restrictions of the chest wall as respiratory stimulation may cause increased ventilatory attempts against a closed airway which may lead to pulmonary edema.
6. AIMS OF THE STUDY

The aim of this thesis was to examine different modalities of sedation for improving the quality of sedation in ERCP procedures. The specific aims of the four studies were:

I: To examine how PCS was adopted into clinical practice in the endoscopy unit and study the differences in the safety profile of different methods of sedation.

II: To compare different methods for assessing the level of propofol sedation during ERCP

III: To assess the usefulness of routine preoperative laboratory testing for ERCP and to find out if some laboratory test results were associated with adverse effects

IV: To study if the respiratory stimulant doxapram could be used as an additive to propofol sedation to decrease the risk respiratory depression during sedation.
7. MATERIALS AND METHODS

7.1. Patients and Study designs

All studies were performed in the endoscopy unit of Helsinki University Central Hospital. The population of this thesis consisted of three different groups of patients. In two of the studies (I, III) the patient group was all 956 adult patients who had ERCP performed on them in the endoscopy unit March 1st, 2012-February 28th, 2013. For study II, 200 patients were recruited during December 11th, 2013 to January 19th, 2016. A total of 56 patients were recruited for the last study (IV) during November and December of 2016.

Studies I-III were prospective observational studies. Studies I and III consisted of the same patient population as mentioned in the previous paragraph. A large prospective database was collected and employed in the studies. All adult patients receiving ERCP in the endoscopy unit of HUCH were included in the studies. ERCP and sedation details and demographic details were recorded and background information on patients’ medication and illnesses were gathered from patient records.

Study II was a prospective study in which four different methods of assessment sedation, mOAAS, modified Ramsay scale (mRSS), RASS and BiS, were simultaneously used on each patient recruited to the study. BiS was selected as the comparator because it is an objective method as opposed to the other scales which rely on the subjective clinical assessment of the other scales. Exclusion criteria for the study were refusal to participate and inability to give an informed consent. All other ERCP patients were eligible for the study.

Study IV was a randomized, double-blinded, placebo-controlled study. A computer-generated random number list was used with sealed non-opaque envelopes. Exclusion criteria for the study were age >75 years, epilepsy, coronary artery disease (stable or unstable angina pectoris), chronic obstructive pulmonary disease, acute alcohol withdrawal syndrome, allergy to propofol or doxapram, refusal to participate in the study, and inability to give an informed consent.
7.2. ERCP

ERCP was performed according to standard clinical practice in all the studies by an experienced endoscopist. Patients were positioned initially in prone position, but adjustments of patient positioning were possible. Carbon dioxide insufflation was used to inflate the intestinal lumen and glucagon and buspirone were administered to reduce intestinal motility when needed. In studies II and IV endoscopist reported satisfaction by a questionnaire examining ease of inserting the duodenoscope, patient co-operation, gagging, coughing, belching, distracting movement by the patient using a four-step scale from none to plenty. The degree of difficulty of the ERCP procedure was assessed by the Schutz scale(4) in all the studies. Antibiotic prophylaxis and rectal diclofenac were given according to institutional practice guidelines.

7.3. Sedation

Three methods of sedation were used in the studies. Sedation was monitored at all times by an anesthesia team consisting of an anesthesiologist and an anesthesia nurse, who intervened when needed.

7.3.1. Patient-controlled sedation

PCS was one possible choice for sedation by the anesthesiologist in studies I, II, And III. PCS was administered according to standard clinical practice of the endoscopy unit. PCS solution contained propofol 8mg/ml and alfentanil 0.06mg/ml. A syringe-driver with a self-administration unit (Syramed μSP6000; Arcomed AG, Regensdorf, Switzerland) was prepared with the PCS solution and the patient could take at will a 1ml i.v. bolus of PCS solution by pressing the button of the self-administration unit. There was no background infusion, lockout time or dose limit. PCS was considered successful, if a patient received sedation only through PCS. Thus, any intervention (i.e. additional sedation) by anesthesia team deemed PCS episode unsuccessful.
7.3.2. Anesthesiologist administered sedation

7.3.2.1. Anesthesiologist administered PCS solution

Anesthesiologist could use the same PCS device and solution as the patient to administer sedation for patients in studies I, II and III. The entire sedation could be administered by the anesthesiologist using the PCS device or in case PCS was not successfully used by the patient the anesthesiologist could take over and stop the self-administration by the patient.

7.3.2.2. Propofol infusion

Propofol infusion was the only option for sedation in study IV and a possible choice in other studies. Propofol 10mg/ml solution was used in all studies.

7.3.3. Doxapram

Use of doxapram to reduce respiratory depression caused by propofol sedation was investigated in Study IV. It was administered as an i.v. infusion of 1mg/kg/h and an initial bolus of 1mg/kg immediately following the induction of sedation by propofol. Additional boluses were given in the event of respiratory depression and hypoxemia. Several patients also received doxapram in studies I and III but most, if not all, of them were in preparation for study IV and not because of acute respiratory depression.

7.3.4. Additional medication

In addition to PCS solution and propofol infusion there were other drugs used to facilitate the procedure. Topical lidocaine spray and intravenous glycopyrronium was part of the protocol in study IV and could be used in other studies according to the clinical judgement of the anesthesiologist. Lidocaine was also part of the lubricant used to ease the swallowing of the duodenoscope. As ERCP can cause significant pain, opioids were administered as needed, fentanyl being usually the first choice and alfentanil occasionally given according preferences of the treating anesthesiologist. Ketamine was also used as needed when deemed necessary by the anesthesiologist. Midazolam and diazepam and naloxone in addition to propofol
were used sporadically in studies I and III and not at all in studies II and IV, so any analysis of their use is unfeasible.

7.4. Routine preoperative laboratory tests

The following laboratory tests were taken from all patients in studies I and III: basic blood count (BBC), electrolytes (P-Na and P-K), thromboplastin time (P-TT) and international normalized ratio (P-INR), amylase levels before the procedure and 4 and 24 h after the procedure.

7.5. Measurements

7.5.1. Primary outcome measures

In study I the primary outcome measures were choice of sedation and successful use of PCS. Correlation of the different sedation scales was the primary outcome measure of study II. BiS was divided to three categories in study II: light sedation, when Bis was over 85, moderate sedation 65 to 85 and deep sedation below 65. Primary end points of study III were adverse effects related to ERCP, sedation or both. In study IV the primary outcome measures were apneic episodes (patient does not breathe for 30 seconds) and hypoxemia (SpO$_2$ below 90 %).

7.5.2. Secondary outcome measures

Secondary outcome measures for study I were respiratory and cardiovascular depression (systolic blood pressure <90mmHg) and the consumption of sedatives and opioids. In study II the secondary outcome measures were method of sedation, sedation related adverse effects and consumption of medication. The secondary outcome measures for study III were laboratory test results, comorbidities and medication of the patients. Anemia, hyponatremia, and thrombocytopenia were defined as test results level below reference values. In study IV the secondary outcome measures were peripheral oxygen saturation (SpO$_2$), blood pressure, heart rate, respiratory rate, end tidal carbon dioxide (EtCO$_2$), BiS, mOAAS and drug
consumption during the procedure, blood pressure, heart rate, respiratory rate, Gilham score and Aldrete score during recovery and patient and endoscopist satisfaction. The need for mask ventilation was recorded in all the studies.

7.6. Statistical analysis

The results are reported as median and interquartile range (Studies I-IV) or mean and standard deviation (Study IV) as appropriate. Logistic regression analysis was used in study I to assess the risk of failure of PCS and the factors affecting the choice of sedation method. It was also used in study III to assess the risk of adverse effects. In both studies forward stepping was used with \( p < 0.05 \) criteria.

In study II Prediction probability and Spearman correlation coefficient were calculated to show the relationships between the studied sedation scales and BiS. Cronbach’s alpha was calculated to determine the consistency of the scales with respect to one another. Multilevel ROC-curves were used to illustrate specificity and sensitivity of the scales in relation to BiS. Spearman correlation coefficient and prediction probability \( P_k \) of the different sedation scales in relation to BiS were calculated to see how well the scales predict the order of two observed sedation scales and endoscopist satisfaction.

In study IV the Mann-Whitney U-test and Fisher’s exact test were used to test the possible differences between the groups. Mixed effects modelling was used to account for repeated measurements on the same subject and comparing results between the groups. For continuous variables a linear model was used and multinomial logistic regression model for ordinal variables. A separate mixed effects model was also used on each group to analyze the possible time dependency within the group. A power analysis was performed before the study. At least 18 patients per group were required to detect a 30\% difference in respiratory depression between the groups (\( \beta = 0.1, \alpha < 0.05 \)).

Statistical calculations were generated using IBM SPSS statistics 19 (International Business Machines Corporation, Endicott, NY, USA) for study I, IBM SPSS Statistics 24 (International Business Machines Corporation, Endicott, NY, USA), Medcalc Statistical software v 17.6 (Ostend, Belgium) and R v 3.3.2 (12) with pROC.
package(13) for study II, IBM SPSS Statistics 21 (International Business Machines Corporation, Endicott, NY, USA) for Study III and IBM SPSS Statistics 24 (International Business Machines Corporation, Endicott, NY, USA) for Study IV.

7.7. Ethical concerns

All studies were conducted according to the WMA declaration of Helsinki and approved by the Ethics committee of Helsinki University Central Hospital (Ethics Committee, Department of Surgery, Biomedicum Helsinki 2 C, Tukholmankatu 8C, PL 705, 00029 HUS, Finland). Studies II and IV were also registered in the Clinicaltrials.gov database and Study IV was approved by the Finnish Medicines Agency (FIMEA) and registered in the EudraCT-system. Informed consent was acquired on the day of the procedure for studies II and IV. The need for informed consent was waived by the ethics committee for studies I and III.
8. RESULTS

A total of 733 patients had PCS with success rate of 77% (565 of 733). AAS with PCS solution was used in 286 patients and AAS with propofol-infusion was used in 429 patients. The demographics of the patients are shown in Table 6. The discrepancy between the number of patients and procedures is due to some patients having more than one ERCP performed on them.

**Table 6. Demographics of the studies**

<table>
<thead>
<tr>
<th></th>
<th>Study I, III</th>
<th>Study II</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>956</td>
<td>200</td>
<td>56</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>529/427</td>
<td>122/78</td>
<td>N/A</td>
</tr>
<tr>
<td>Age, years, median (IQR)</td>
<td>59 (25)</td>
<td>56 (25.3)</td>
<td>49 (18)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.0 (6.2)</td>
<td>25.0 (4.9)</td>
<td>25.7 (6.9)</td>
</tr>
<tr>
<td>ASA class, I/II/III/IV/V</td>
<td>35/417/582/160/2</td>
<td>10/86/69/35/0</td>
<td>5/29/21/0/0</td>
</tr>
</tbody>
</table>

IQR=interquartile range, ASA class=American Society of Anesthesiologists physical status classification
8.1. ERCP details

Details of ERCP in each study are shown in Table 7. Patients usually have several procedures done on them during ERCP. The difficulty of ERCP according to Schutz scale in Study I and III was grade 1: 332 (28%), grade 2: 484 (41%), grade 3: 325 (27%) and Grade 4: 52 (4%), in study II: grade 1: 112 (56%), grade 2: 28 (14%) and grade 3: 60 (30%) and in study IV: grade 1: 35 (62%), grade 2: 4 (7%) and grade 3: 17 (30%)

Table 7. ERCP details in the studies I-IV

<table>
<thead>
<tr>
<th>ERCP procedure</th>
<th>Study I, III Number (%)</th>
<th>Study II Number (%)</th>
<th>Study IV Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary cytology</td>
<td>416 (35)</td>
<td>79 (40)</td>
<td>26 (46)</td>
</tr>
<tr>
<td>Biliary sphincterotomy</td>
<td>562 (47)</td>
<td>49 (25)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Common bile duct stone extraction</td>
<td>345 (29)</td>
<td>16 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Biliary dilatation</td>
<td>164 (14)</td>
<td>29 (15)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Biliary stent application, exchange or removal</td>
<td>357 (30)</td>
<td>51 (26)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>207 (17)</td>
<td>7 (4)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Pancreatic cytology</td>
<td>35 (3)</td>
<td>5 (3)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Pancreatic dilatation</td>
<td>101 (8)</td>
<td>16 (8)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Pancreatic stent application, exchange or removal</td>
<td>216 (8)</td>
<td>33 (17)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Pseudocystogastrostomy or duodenostomy</td>
<td>24 (2)</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Peroral cholangioscopy</td>
<td>21 (2)</td>
<td>5 (3)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Double balloon ERCP</td>
<td>8 (1)</td>
<td>6 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Procedure duration, minutes, median (IQR)</td>
<td>23 (19)</td>
<td>23.5 (17.3)</td>
<td>20 (16)</td>
</tr>
</tbody>
</table>
8.2. Adverse effects of ERCP

The rate of ERCP related adverse effects in the study population included in studies I and III was 8.9% (107 adverse effects in 1196 procedures) when all the procedures and generally accepted adverse effects were accounted for. Adverse effects related to ERCP are shown in Table 8. Milder forms of adverse effects, such as pain in the stomach and nausea are not considered ERCP-related adverse effects in this context.

Table 8. Adverse effects related to ERCP in studies I and III

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>43 (3.6)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>17 (1.4)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>17 (1.4)</td>
</tr>
<tr>
<td>Periampullary perforation</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Miscellaneous (pseudocyst infection, air embolism, stent rupture, etc.)</td>
<td>19 (1.6)</td>
</tr>
<tr>
<td>Cardiopulmonary (myocardial infarction, pulmonary embolism)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Mortality, 1-day</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Mortality, 1-week</td>
<td>10 (0.8)</td>
</tr>
<tr>
<td>Mortality, 30-day</td>
<td>44 (3.7)</td>
</tr>
</tbody>
</table>
8.3. Adverse effects related to sedation

A total of 247 patients (17 %) presented with adverse effects related to sedation. The most common adverse effect was respiratory depression and its frequency was twice as high in study IV compared to that in study I (and III). The overall rate of adverse effects is shown in Table 9.

Table 9. Sedation related adverse effects in studies I-IV

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Study I, III, n (percentage)</th>
<th>Study II, n (percentage)</th>
<th>Study IV, n (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>128 (11)</td>
<td>5 (3)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Mask ventilation</td>
<td>15 (1)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cardiovascular depression</td>
<td>86 (7)</td>
<td>15 (8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
PCS was used to sedate patients in studies I-III. Table 10 illustrates the sedation related adverse effects when PCS was the method of sedation.

### Table 10. Adverse effects for patient-controlled sedation in studies I, II and III

<table>
<thead>
<tr>
<th>Studies (number of patients)</th>
<th>Respiratory depression, n (percentage)</th>
<th>Mask ventilation, n (percentage)</th>
<th>Cardiovascular depression, n (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS, overall (733)</td>
<td>71 (9.7)</td>
<td>10 (1.4)</td>
<td>42 (5.7)</td>
</tr>
<tr>
<td>PCS, successful (565)</td>
<td>46 (8.1)</td>
<td>2 (0.4)</td>
<td>22 (3.9)</td>
</tr>
<tr>
<td>PCS, unsuccessful (168)</td>
<td>25 (14.9)</td>
<td>8 (4.8)</td>
<td>20 (11.9)</td>
</tr>
</tbody>
</table>

PCS=patient-controlled sedation
Propofol infusion was used in all the studies. Both PCS solution administered by the anesthesiologist using the PCS device and propofol infusion were chosen according to the clinical judgement and preferences of the treating anesthesiologist. Sedation related adverse effects with anesthesiologist administered sedation are illustrated in table 11. Cardiovascular depression and respiratory depression were detected with equal frequency in AAS patients.

Table 11. Adverse effects for anesthesiologist administered sedation in studies I-IV

<table>
<thead>
<tr>
<th>Studies (number of patients)</th>
<th>Respiratory depression, n (percentage)</th>
<th>Mask ventilation, n (percentage)</th>
<th>Cardiovascular depression, n (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS by anesthesiologist (286)</td>
<td>30 (10,5)</td>
<td>1 (0,3)</td>
<td>26 (9,1)</td>
</tr>
<tr>
<td>Propofol infusion (429)</td>
<td>45 (10,5)</td>
<td>6 (1,4)</td>
<td>33 (7,7)</td>
</tr>
</tbody>
</table>

PCS = Solution used for patient-controlled sedation

8.4. Patient-controlled sedation

Patients sedated with PCS required less propofol for ERCP than patients treated with AAS. Median (IQR) consumption of propofol for PCS was 140 (110) mg and 189 (216) mg for other sedation methods in study I and III and 176 (76) mg and 197 (210) mg for other methods in study II (p<.001 in both studies). Patients in Studies I-III also received a lighter sedation with PCS than other methods of sedation (p<0.001). There were no statistically significant differences in Fentanyl consumption between the groups in either study. PCS group received more alfentanil due to PCS solution in
both studies \(p<.001\), but the use of additional boluses was so rare that statistical analysis was not feasible. There was no statistically significant difference in the duration of the procedure in either study with regard to PCS vs. AAS \(p=.1\) and \(p=.18\) in studies I/III and II, respectfully). In study II patient and endoscopist satisfaction was high in both groups with no statistical differences. The level of sedation was lighter with PCS than AAD in studies I-III \(p<.001\).

### 8.5. Sedation scales

All sedation scales used reliably assessed the sedation level. Table 12 shows the results of Cronbach’s alpha for the different sedation scales.

#### Table 12. Cronbach’s alpha, including mOAAS, RASS, mRSS, BiS

<table>
<thead>
<tr>
<th>Variable dropped:</th>
<th>mOAAS</th>
<th>RASS</th>
<th>mRSS</th>
<th>BiS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>0.9406</td>
<td>0.9018</td>
<td>0.9114</td>
<td>0.9745</td>
</tr>
<tr>
<td>Change</td>
<td>-0.0314</td>
<td>0.03174</td>
<td>0.03645</td>
<td>0.04094</td>
</tr>
<tr>
<td>95% lower confidence limit</td>
<td>0.9381</td>
<td>0.9018</td>
<td>0.9114</td>
<td>0.9745</td>
</tr>
</tbody>
</table>

mOAAS = modified observer’s assessment of agitation and sedation, RASS = Richmond Agitation/Sedation scale, mRSS = modified Ramsay sedation scale, BiS = Bispectral index
Observational scales were all statistically significantly correlated with BiS. Number of data points per patient for each variable was 6 (3,25). $P_K$ and Spearman correlation coefficient of the scales compared to BiS are shown in Table 13.

**Table 13. Prediction probability $P_K$ and Spearman correlation coefficients**

<table>
<thead>
<tr>
<th></th>
<th>mOAAS</th>
<th>RASS</th>
<th>mRSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somer's D</td>
<td>0.40</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>SE</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>p</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>$P_K$</td>
<td>0.699</td>
<td>0.697</td>
<td>0.695</td>
</tr>
<tr>
<td>SE</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Spearman correlation coefficient</td>
<td>0.695</td>
<td>0.6783</td>
<td>0.673</td>
</tr>
<tr>
<td>SE</td>
<td>0.016</td>
<td>0.017</td>
<td>0.017</td>
</tr>
<tr>
<td>p</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

$mOAAS$ = modified observer’s assessment of agitation and sedation, $RASS$ = Richmond Agitation/Sedation scale, $mRSS$ = modified Ramsay sedation scale, SE = standard error,
8.6. Routine preoperative laboratory testing

RPLT was done to all patients but could not predict adverse effects related ERCP in study III. The results of the RPLT are shown in table 14.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result, median (IQR)</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (B-Hb, g/L):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-males</td>
<td>135 (29.5)</td>
<td>134-167</td>
</tr>
<tr>
<td>-females</td>
<td>122 (20)</td>
<td>117-155</td>
</tr>
<tr>
<td>Platelet count (10E9/L)</td>
<td>243 (126)</td>
<td>150-360</td>
</tr>
<tr>
<td>Potassium (P-K, mmol/L)</td>
<td>3.9 (0.53)</td>
<td>3.3-4.9</td>
</tr>
<tr>
<td>Sodium (P-Na, mmol/L)</td>
<td>139 (4)</td>
<td>137-145</td>
</tr>
<tr>
<td>Thromboplastin time (P-TT, %)</td>
<td>95 (41)</td>
<td>70-130</td>
</tr>
<tr>
<td>International Normalized Ratio (P-INR)</td>
<td>1.1 (0.2)</td>
<td>2-3 (patients on anticoagulants)</td>
</tr>
</tbody>
</table>

Adverse effects related to sedation were associated with some laboratory test results. Anemia was associated with fewer respiratory depression incidents (OR 0.26, p<.001) if the patient had no cardiovascular disease. Hyponatremia (OR 2.22, p=.001) and thrombocytopenia (OR 1.87, p=.025) were found to be risk factors for cardiovascular depression, and men with hyponatremia (OR 3.66, p<.001) presenting greater risk compared to women with hyponatremia (OR 1.09, p=.078).
8.7. Doxapram

All 56 patients recruited in Study IV completed the study and were included in the analysis. Doxapram was not found to be effective in reducing respiratory depression in study IV. There were no statistically significant differences between the group receiving doxapram (group DOX) and the control group (Group P). Doxapram did not reduce the incidence of either apneic episodes (20 in 17 patients in group P, 15 in 11 patients in group DOX, p=.18) or hypoxemia (7 in 5 patients in group P, 11 in 8 patients in group DOX, p=.53). Additional doxapram boluses were given in both groups (3 in group P and 1 in Group DOX, p=.61). Doxapram did not have any effect on patient recovery or patient and endoscopist satisfaction. No adverse effects attributable to doxapram was observed.
9. DISCUSSION

The present results show that PCS with propofol / alfentanil -mixture was feasible sedation protocol for ERCP. The present study suggests that there may be fewer adverse effects with PCS compared to those with AAS. RPLT was not able to detect patients prone to adverse effect of ERCP. In addition to observational scales, the level of sedation is possible to monitor with EEG -based BiS.

9.1. Patient-controlled sedation

PCS has been shown to be a viable option for sedation during ERCP in previous studies(78, 79) and this was further confirmed in the studies I-III. Patient and endoscopist satisfaction were recorded in study II and they were comparable to AAS, both were very high. There were not any statistically significant differences in sedation related adverse effects between PCS and propofol infusion in studies I and III. PCS showed favorable cardiovascular profile in Study II compared to AAS. These findings are in accordance with other studies(74). This discrepancy can be explained by the amount of propofol the patients received during sedation. Patients using PCS successfully administered half the amount of propofol when compared to propofol infusion. According to the meta-analysis by Kreienbühl from 2018(74) there was no difference in propofol consumption with PCS and AAS. However, that meta-analysis was about PCS in general and not exclusive to endoscopy. The clinical practice of sedation for ERCP in our clinic tends to be a very deep propofol sedation which explains the difference. PCS also led to lower levels of sedation, which while not affecting the duration of ERCP significantly may well lead to more rapid recovery times and thus lower total health care costs.

All that being said, there are still problems with PCS. PCS requires the patient to take charge of their sedation. While the method is relatively simple, the patient must be well informed on the mechanics of PCS and even early phases of dementia may impair cognition sufficiently that PCS is not feasible, especially during sedation. Some discomfort must also be accepted by the patient since the sedation is delivered on demand and the level of discomfort varies quite a bit during ERCP. However, patient satisfaction seems to be high and comparable to AAS despite this (78, 79).
9.2. Assessment of sedation level

Study II found that all the studied sedation scales had good correlation with each other. As such all of them can be used to assess depth of sedation during ERCP. An issue with the sedation scales currently used in clinical practice is the lack of objectivity. These scales are dependent on the subjective assessment of the clinician observing the patient. While the scales are generally found to have good inter-observer validity and reliability\cite{113, 114}, the lack of objectivity may result in poor sedation.

There are EEG-based depth of anesthesia monitors in clinical use, such as BiS, E-Entropy, Narcotrend and qCON. Of these, BiS has been used most in clinical research for endoscopic sedation. These monitors do not require the patient to react to specific stimuli and as such facilitate uneventful procedures and sedation. Also, the depth of sedation can be titrated more accurately than by clinical observation of the anesthesia provider since arousal can be observed before the patient regains consciousness. However, the actual clinical impact of EEG-based depth of sedation monitoring has not been shown in current research. While studies tend to show more stable level of sedation and lower consumption of sedatives, the clinical outcomes, i.e. adverse effects such as cardiovascular and respiratory depression tend not to be improved with statistical significance\cite{29, 30}. The objective nature of these monitors is a point in their favor as opposed to the subjective assessment of sedation using more traditional sedation scales.

There are several guidelines regarding sedation for gastrointestinal endoscopy and they all instruct clinicians to assess the level of sedation in some manner (13-15, 23, 115, 116). There is no consensus on the method of assessment though, and there is a lot of variation in the practices of assessing sedation level in different clinics and countries\cite{117}.

One problem with assessment of sedation is the fact, that most sedation scales are developed for use in the intensive care setting and validated for that use and not for procedural sedation. The problem arises when the scales used require a response to certain stimuli such as response to verbal command. If the patient is adequately sedated before determining the level of sedation, the arousal caused by the assessment may cause the level of sedation to become inadequate during a
procedure. While the arousal is not problematic in the intensive care unit and usually is even the desired effect(118), it may be detrimental during a demanding endoscopic procedure such as ERCP, which is another point in favor of EEG-based depth of anesthesia monitors.

**9.3. Preoperative laboratory testing**

Study III added confirmation to the current trend of eliminating unnecessary laboratory testing preoperatively. Both AGSE(101) and the British NICE guidelines(119) advice against routine preoperative laboratory testing. The NICE guideline is about elective surgery but can be extrapolated from that setting into endoscopy. Even the AGSE guideline is forced to extrapolate the findings from surgical series since the scientific literature concerning endoscopy is limited in this setting.

Even before Study III, there were plenty of studies advocating for elimination of routine preoperative testing for surgery(91, 120-123). According to these studies the use of RPLT is not cost effective and may even be harmful to the patient. An innocuous abnormality may lead to unnecessary further testing and may expose the patient to risks such as delays to necessary procedures due to controlling harmless abnormalities in test results or infection from blood sampling.

As RPLT has not been found to effectively predict adverse effects, the practice should be eliminated, and it would seem prudent to limit laboratory testing before ERCP to select groups of patients and to prescribe only the tests that are clinically relevant. This change in practice may lead to significant financial savings in the long run.

**9.4. Doxapram**

Doxapram was not found to be effective in reducing respiratory depression in study IV. There were fewer patients with apneic episodes and patients requiring additional doxapram boluses in the doxapram group, but more patients with hypoxemia in that group. No statistically significant differences were found between the groups in any of the primary outcomes. There is a possibility of a type II error, since the number of
patients in the study was limited, but these findings do not warrant a larger study with the same protocol.

The dosage of doxapram used in study IV was quite low, while still within the doses given in previous studies\(^\text{102}\). This was done in order to avoid the possible analeptic effect of doxapram. It is possible that using a higher dose could have yielded a more favorable outcome. After all, the amount of doxapram the patients received was well below the toxic level of 130mg/kg/day and lower than the dosages used for respiratory failure before more modern ventilatory systems.

It is also worth noting, that the level of sedation used in study IV was very deep, practically general anesthesia. A moderate level of sedation for ERCP has been used in several studies, corresponding to BiS level of approximately 60-80\(^{28, 124, 125}\). A lower level of sedation would most likely lead to less profound respiratory depression and enable doxapram to have the desired stimulatory effect with the chosen dosage.

9.5. Limitations

There are some limitations in these studies. All the studies were single center studies, so their applicability may not be universal. In study I the reason for selection of sedation method was not recorded and the lack of randomization may have on effect on the results. In study II the level of sedation was not determined beforehand but decided on a case-by-case basis by the attending anesthesiologist which limits the scope of the study to the comparison of the studied sedation scales and cannot be used to determine other modalities, such as the optimal level of sedation for ERCP. In study III the amount of some adverse effects was so low that the statistical analysis of their risk factors and was not feasible. The number of patients in study IV was relatively low, which does not enable conclusions about the efficacy of the treatment with certainty. Exclusion criteria can also influence the results of study IV.
10. CLINICAL IMPLICATIONS AND FUTURE CONSIDERATIONS

The most important finding was that it is safe and economical to forgo routine preoperative laboratory testing and switch to prescribing laboratory testing only as needed based on the needs of the individual patient or some beforehand determined patient population (study III). This will reduce the costs of health care and the inconvenience caused to the patient by excessive laboratory testing.

Study I found that PCS was an acceptable method for sedation for ERCP with a safety profile comparable to traditional propofol sedation in normal clinical practice. As none of the studied methods of sedation was found to be superior when compared to others, an optimal choice of sedation for ERCP could not be determined.

Study II provides data to clinicians on how to assess the level of sedation during procedural sedation. As guidelines recommend recording the sedation level in anesthesia records, it cannot be ignored, and study II provides some tools to do it. While there is no consensus on what method should be used to assess the depth of sedation during ERCP, study II shows that all the scales used in the study can be used. As discussed above, it may be that BiS is the most useful of these scales, but further studies are needed, also using other EEG-based depth of anesthesia monitoring devices. Also, study II was not set up to find an optimal sedation level to aim for during ERCP which is a very important question that remains to be answered.

Doxapram was not found to be effective in reducing respiratory depression during deep propofol sedation for ERCP (study IV). Further studies with different dosing regimens and sedation depths could give the answer whether doxapram has a place in modern sedation practice for endoscopies. In recent years a new exciting possibility has emerged(126, 127). High flow nasal oxygenation (HFNO) can be used to oxygenate patients in apnea for up to 45 minutes. Naturally this needs to be studied further, but if such apnea times can be safely reached during ERCP with HFNO, the need for respiratory stimulants will be non-existent.
11. CONCLUSIONS

There are several conclusions that can be derived from the data of this thesis.

1. Patient-controlled sedation and anesthesiologist administered sedation are both acceptable methods of sedation for ERCP. The method of choice is determined by the preferences of the anesthesia provider and the individual characteristics of the patient.

2. BiSpectral index, modified observer's assessment of agitation/sedation, Richmond agitation sedation scale and the Ramsay sedation scale are all valid methods of assessing the level of sedation during ERCP. However, BiSpectral index being objective and requiring no interaction with the patient is preferable in clinical practice.

3. Routine preoperative laboratory testing should be abandoned, and tests should be prescribed individually based on the individual characteristics of the patient.

4. Doxapram infusion (1mg/kg/h) does not reduce respiratory depression caused by deep propofol sedation during ERCP
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Jarno Jokelainen
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