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PATIENT-CONTROLLED SEDATION FOR ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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ACADEMIC DISSERTATION

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In memoriam of Vera, Dmitry, Elena and Nikolaj

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1 ABSTRACT

Endoscopic retrograde cholangiopancreatography (ERCP) is the radiographic examination of the biliary and/or pancreatic ductus via endoscopically cannulated duodenal papilla. ERCP is one of the common procedures performed in the gastrointestinal (GI) endoscopy suite and for its successful performance adequate sedation and analgesia are rather necessary than desired. During the last decade propofol alone or in combination with an opioid replaced traditionally used benzodiazepines and became the most preferred sedative agent during ERCP. The method of choice for the safe and cost-effective sedation of patients with spontaneous respiration during GI endoscopy is still to be defined. Self administration of propofol by the patients (patient-controlled sedation, PCS) might be one of the possibilities of this kind. Dexmedetomidine has gained approval for procedural sedation of non-intubated patients and has been reported effective in the treatment of alcohol withdrawal. The suitability of dexmedetomidine for sedation of alcoholics during ERCP has not been previously evaluated.

Four prospective randomized control trials consisting of 293 ERCP patients were performed in the Endoscopy unit of the Helsinki University Central Hospital from January 2009 to January 2011. PCS was compared with anesthesiologist administered sedation (AAS) using manually adjusted propofol infusion (**I**) and target-controlled infusion (TCI) system (**III**). Remifentanyl and alfentanil were compared double-blindly in sedative mixture for PCS (**II**) and dexmedetomidine was evaluated for sedation of patients with chronic alcoholism in placebo-controlled double-blind study (**IV**).

In all studies (**I-IV**) self-administration device was adjusted to deliver 1ml single bolus-dose of propofol or propofol-opioid mixture without any lockout time, background infusion or total dose limitation. PCS was considered as successful if propofol was not administered by anesthesiologist and/or ERCP was not interrupted due to sedation related complication. Loading dose of 1 mcg · kg⁻¹ of dexmedetomidine was infused 10 minutes before ERCP start thereafter maintenance infusion at the constant rate of 0.7 mcg · kg⁻¹ · h⁻¹ was continued until the end of procedure (**IV**). In control groups sedation was administered by anesthesiologist with the use of manually adjusted propofol infusion (**I**) or target-controlled propofol infusion with initial effect effect-site concentration 2 mcg · ml⁻¹ (**III**). Patients were monitored according to the standard of monitoring for deep sedation. Additionally end-tidal carbon dioxide and sedation levels with the use of sedation scales were followed. Hypoxemia (peripheral oxygen saturation below 90 % of any duration), respiratory depression (respiratory rate < 6 /min), hypotension (systolic blood pressure below

90 mmHg), arrhythmia, and pulmonary aspiration were considered as sedation related adverse events (SRAE).

Consumption of propofol was the main outcome measure in all studies. Secondary objectives were success rate of PCS, SRAE, patient satisfaction with sedation, easiness of ERCP performance, and rapidity of the recovery.

With the use of PCS propofol consumption was significantly lesser than with AAS using either manually adjusted or target-controlled propofol infusion. The success rate of PCS was 88 -100 %. The incidence of SRAE, easiness of ERCP performance, and patient satisfaction with sedation were similar during PCS and AAS. Patients who received PCS gained faster recovery than those who received AAS. Both alfentanil and remifentanil showed good suitability for PCS during ERCP without significant difference in propofol consumption, patient satisfaction and rapidity of the recovery. However, in combination with propofol remifentanil depressed spontaneous respiration more frequently and produced significantly more nausea post-procedurally. Increase of alfentanil concentration in sedative mixture from $0.04 \text{ mg} \cdot \text{ml}^{-1}$ to $0.08 \text{ mg} \cdot \text{ml}^{-1}$ did not provide any demonstrable benefit. The studied regimen of dexmedetomidine administration showed poor suitability for sedation of alcoholics during ERCP either alone or in combination with PCS because of prolonged induction of sedation, insufficient sedative effect, significant reduction of PCS success rate and slow recovery. Instead, PCS with propofol and alfentanil might be very successful for sedation of alcoholics during ERCP. 93 % of patients preferred PCS as a sedation method for possible future ERCP.

In conclusion, PCS with combination of propofol and alfentanil is recommended as a primary method of sedation during ERCP.

2 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by the Roman numerals I to IV.

- I** Mazanikov M, Udd M, Kylänpää L, Lindström O, Aho P, Halttunen J, Färkkilä M, Pöyhiä R. Patient-controlled sedation with propofol and remifentanyl for ERCP: A randomized, controlled study. *Gastrointest Endosc* 2011; 73: 260-266.
- II** Mazanikov M, Udd M, Kylänpää L, Mustonen H, Lindström O, Halttunen J, Färkkilä M, Pöyhiä R. Patient-controlled sedation for ERCP: A randomized double-blind comparison of alfentanil and remifentanyl. *Endoscopy* 2012; 44: 487-492.
- III** Mazanikov M, Udd M, Kylänpää L, Mustonen H, Lindström O, Halttunen J, Färkkilä M, Pöyhiä R. A randomized comparison of target-controlled propofol infusion and patient-controlled sedation during ERCP.
- IV** Mazanikov M, Udd M, Kylänpää L, Mustonen H, Lindström O, Halttunen J, Pöyhiä R. Dexmedetomidine impairs success of patient-controlled sedation in alcoholics during ERCP: a randomized double-blind and placebo-controlled study. *Surg Endosc* 2013 Jan 26. [Epub ahead of print]

Some unpublished data included

3 ABBREVIATIONS

AAS = anesthesiologist administered sedation;

ASA = American Society of Anesthesiology;

BMI = body mass index;

CI = confidence interval;

C_E = effect-site concentration;

C_p = plasma concentration;

CV = coefficient of variation;

ECG = electrocardiography;

EGD = esofagogastroduodenoscopy;

ERCP = endoscopic retrograde cholangiopancreatography;

EtCO_2 = end-tidal carbon dioxide;

EUS = endoscopic ultrasound;

ICU = intensive care unit;

ISTF = International Sedation Task Force;

GA = general anesthesia;

GI = gastrointestinal;

HR = heart rate;

$\text{l} \cdot \text{min}^{-1}$ = liters per minute;

MAC = monitored anesthesia care;

MC = manually controlled;

min = minutes;

mg = milligrams;

$\text{ml} \cdot \text{h}^{-1}$ = millilitres per hour;

mcg = micrograms;

$\text{mg} \cdot \text{ml}^{-1}$ = micrograms per millilitre;

$\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ = micrograms per kilogram per minute;

MOAA/S = Modified Observer's Assessment of Alertness and Sedation;

mmHg = millimetre of mercury;

n = number of patients;

NAPS = nurse administered propofol sedation;

NIBP = non-invasive blood pressure;
PCS = patient-controlled sedation;
PI = propofol infusion;
PPC = propofol plasma concentrations;
PMS = patient-maintained sedation;
RASS = Richmond Agitation-Sedation Scale;
RR = respiratory rate;
SD = standard deviation;
SIVA = Society of Intravenous Anesthesia;
SpO₂ = peripheral oxygen saturation;
SRAE = sedation related adverse events;
TCI = target-controlled infusion;
US = United States;
VAS = visual analogue scale;
VRS = verbal rating scale;
WMA = World Medical Association.

4 INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a complex gastrointestinal endoscopic procedure that involves cannulation and radiographic imaging of the biliary tree and pancreatic duct and is used in the diagnosis and treatment of a wide spectrum of biliary and pancreatic disorders. The procedure is started with the insertion of duodenoscope and filling the stomach and small intestine with air or carbon dioxide; thereafter the duodenal papilla is accessed for cannulation. At this stage and, if needed, during consequent procedure, glucagon is often administered intravenously in order to inhibit duodenal motility. After papilla cannulation contrast media is injected through the catheter under fluoroscopic monitoring for visualization of biliary or pancreatic duct system. Sphincterotomy of the bile or pancreatic duct might be performed in order to facilitate stent placement or removing of the stones. Existing biliar/pancreatic stricture may be dilated with the use of hydrostatic wire-guided balloon. Dilation of pancreatic duct is often very painful while sphincterotomy and biliar dilations are significantly less painful. It is believed that other stages of ERCP do not produce marked painful stimulation. ERCP duration differs markedly (range 10-120 minutes) depending on skills of endoscopist and complexity of procedure. In most difficult cases, such as altered gastrointestinal anatomy, duration of ERCP usually exceeds 90 minutes (Osoegawa T et al. 2012).

The diagnostic and therapeutic utility of ERCP has been demonstrated in the diagnosis and management of choledocholithiasis, primary sclerosing cholangitis, chronic pancreatitis, biliary and pancreatic neoplasm, and biliary perioperative complications. ERCP has been practiced for over 30 years being firstly described in 1968. In excess of several 100.000 of this procedures are performed annually worldwide with possible demand only for China as much as 1 million annually (Liao Z et al. 2013).

ERCP has a complication rate of 5 % -10 % and mortality rate of 0.1 % - 1 % (Williams E et al. 2007). Reported complication rates vary widely because of differences in definitions of complications and patient population. Complications include acute pancreatitis, hemorrhage, perforation, infection (cholangitis, cholecystitis, endocarditis), cardiopulmonary and miscellaneous (Anderson MA et al. 2012). Pancreatitis is the most common of serious ERCP complications. Often occurred transient increase in serum pancreatic enzymes does not constitute pancreatitis. The incidence of post-ERCP pancreatitis ranges widely (1.6 -15.7 %) depending on patient selection. The rate of post-ERCP hemorrhage is 1-1.5 % and is primarily related to sphincterotomy. Hemorrhage may be immediate or

delayed up to 2 weeks. Most ERCP-associated bleeding is intraluminal and mild in origin, also intraductal bleeding and hematomas (hepatic, splenic, and intra-abdominal) can occur. Perforation complicates 0.1-0.6 % of ERCPs procedures. Malignancy and precut access were associated with an increased risk of perforation (Williams E et al. 2007). The incidence of post-ERCP cholangitis does not exceed 1 %. Cholecystitis complicates approximately 0.2 - 0.5 % of ERCPs. Significant cardiopulmonary complications (cardiac arrhythmia, hypoxemia, aspiration) occur in 1 % of ERCP patients with associated mortality 0.07 % (Andriulli A et al. 2007). In the study of Fisher 8 % of patients older than 65 years of age sustained myocardial injury with most injury occurred during prolonged procedures (Fisher L et al. 2006). Cardiopulmonary complications may also arise from medications used for sedation and analgesia. The overall mortality rate after diagnostic ERCP is 0.2 % being twice as high (0.4 %-0.5 %) after therapeutic ERCP. A wide variety of miscellaneous complications may occur: ileus, hepatic abscess, pneumothorax/pneumomediastinum, perforation of colonic diverticulum, duodenal hematoma, portal venous air, impaction of therapeutic devices, pseudocyst infection, stent migration, stent occlusion, liver abscess, and acute cholecystitis.

Undoubtedly, ERCP is a one of the most complex and time-demanding procedures among gastrointestinal endoscopies. Patients are required to stay completely still during uncomfortable and sometimes painful procedure because any inappropriate movement can affect the success of ERCP. For better toleration of ERCP patients receive sedatives and/or analgesics. Recently the use of sedation or general anesthesia was reported in 100 % of ERCP at least in Spain and Greece (Triantafillidis J et al. 2013). Adequate sedation during ERCP is indispensable because insufficient sedation may result in patient discomfort, adverse physiological responses or even injury. On the other hand, excessive sedation may cause dangerous cardio-respiratory depression and loss of protective airway reflexes. Sedation with propofol during ERCP is superior to traditionally used benzodiazepines mainly because of significantly faster recovery (Garewal D et al. 2012, Bo LL et al. 2011). However, such important issues as the targeted level of sedation, the appropriate use and method of administration of sedative drugs during ERCP are unanswered and providing of adequate sedation is based mostly on clinical experience.

5 REVIEW OF THE LITERATURE

5.1 SEDATION AND ANALGESIA IN GASTROINTESTINAL ENDOSCOPY

A wide range of gastrointestinal (GI) endoscopy procedures are carried out in an endoscopy unit. Procedures range from minimally invasive (colonoscopy) to much more invasive and complex such as ERCP and endoscopic submucosal resection. Sedation and analgesia are integral parts of each GI endoscopy procedure (Cohen LB et al 2010). Sedation is defined as a drug-induced depression of the level of consciousness. American Society of Anesthesiologists has defined three levels of sedation with continuity to general anesthesia (Table I).

Functions	Minimal sedation (anxiolysis)	Moderate sedation (analgesia, conscious sedation)	Deep sedation (analgesia)	General anesthesia
Responsiveness	normal verbal response	purpose response to speech or physical stimuli	purpose response to repeated or painful stimuli	no response to pain
Spontaneous ventilation	unaffected	unaffected	may be inadequate	inadequate
Airway	unaffected	unaffected	intervention may be needed	interventions needed (mask, intubation, mechanical ventilatory support)
Cardiovascular functions	unaffected	usually unaffected	usually unaffected	may be impaired (hypotension, bradycardia)

At the level of minimal and moderate sedation patients are able to make purposeful response to verbal stimulation and as a rule, have unaffected respiration and hemodynamics. In contrast, deeply sedated patients are unable to communicate verbally and respond only to painful stimuli. Also spontaneous respiration and hemodynamics can be affected more frequently at the level of deep sedation. Airway and hemodynamic support may be required in deep sedation. Sedation represents a continuum - the cascade of events with progressive alteration in level of responsiveness (ASA practice guideline 2002, Green and Mason 2010). The transition from one sedation level to another may occur with the currently used sedation techniques. It can be difficult to control the required level of sedation because of patient's individual response to sedatives and to nociceptive stimuli.

Therefore, health professional involved in the administration of sedation should possess the skills to recognize sedation related problems and rescue a patient from reached deeper sedation level than it was initially intended.

The main purposes of sedation and analgesia during gastrointestinal endoscopy are to relieve patient's discomfort, pain and anxiety, to reduce memory of unpleasant event and to facilitate procedural performance. Mild to moderate sedation is commonly given by the endoscopist but an anesthesia team is usually required for deep sedation (Riphaus A et al. 2009).

5.1.1 BENZODIAZEPINES AND OPIOIDS

In Europe, US, Canada and Japan majority of GI endoscopies typically performed under moderate sedation (ASA, practice guideline 2002) with benzodiazepines alone or in combination with an opioid. Benzodiazepines are the most often used sedation agents by endoscopists of Italy, Greece and Switzerland (Fanti L et al. 2011). Benzodiazepines do not provide analgesia and for this reason they are commonly co-administered with opioids. In the recent nationwide survey from Germany the use of benzodiazepine and opioid combination was reported in 35 % of GI endoscopies (Riphaus A et al. 2010). Serious adverse effects of benzodiazepines are rare: dose-dependent respiratory depression may occur especially in patients with underlying respiratory disease and sedated with combination of benzodiazepines and opioid (Cohen LB et al. 2007). Flumazenil and naloxone are available antagonists for benzodiazepines and opioids, respectively.

Midazolam and diazepam are the most commonly used benzodiazepines with comparable efficacy of sedation (Faigel DO et al. 2002). Midazolam has been reported more suitable than diazepam because of better amnesic properties, shorter duration and faster onset of action (Ginsberg GG et al. 1992, Macken E et al. 1998, Waring J et al. 2003). A double-blind placebo-controlled evaluation of oral midazolam for premedication of patients undergoing upper endoscopy showed a high efficacy in reduction of anxiety and improving procedural tolerance with a good safety profile (Mui LM et al. 2005).

Comparison of alfentanil/midazolam with midazolam alone for upper GI endoscopy showed improvement in procedural performance and a shorter recovery time in patients received combination of midazolam and alfentanil (Milligan KR et al. 1988). Comparison of midazolam/meperidine with midazolam alone during colonoscopy showed significantly less pain and a higher rate of willingness to repeat the intervention without difference in SRAE in patients received midazolam/meperidine (Radaelli F et al. 2003).

For many years meperidine was the primary choice in GI endoscopy (Keeffe EB et al. 1990). During the last decade fentanyl, alfentanil and remifentanil have

appeared as good alternatives for GI sedation in a number of studies (Cohen LB et al. 2004, el-Bitar N and Sfeir S 2006, Ishido S et al. 1992, Fanti L et al. 2009, Fanti L et al. 2013, Liu S et al. 2009, Mandel J et al. 2008, Mandel J et al. 2010, Akcaboy ZN et al. 2006).

5.1.2 PROPOFOL

Propofol is an intravenous anesthetic with a dose-related sedative and hypnotic properties but only minimal analgesic effect (Smith et al. 1994). The drug has a rapid onset of action, is short acting and rapidly metabolized by the liver (Table III). Very rapid onset and short duration of action make it a suitable sedative for gastrointestinal endoscopy (Patterson KW et al. 1991, Carlsson U et al. 1995, Koshy G et al. 2000, Reimann FM et al. 2000, Sipe BW et al. 2002, Weston B.R. et al. 2003, Faga E et al. 2012).

Compared with benzodiazepines, propofol presents similar rate of adverse effects (Kongkam P et al. 2008, Riphaus A et al. 2005, Vargo JJ et al. 2002, Wehrmann T and Riphaus A 2008, Jung M et al. 2000, Schilling D et al. 2009, Singh H et al. 2008, McQuaid KR and Laine L 2008, Qadeer MA et al. 2005), but provides higher patient satisfaction (Jung M et al. 2000, McQuaid KR and Laine L 2008, Dewitt J et al. 2008), and decreases both sedation induction and recovery time (McQuaid KR 2008, Mandel J et al. 2008, Singh H et al. 2008, Ulmer BJ et al. 2003, Vargo J et al. 2002, Riphaus A et al. 2006). Propofol sedation may increase the quality of endoscopic examination (Jung M et al. 2000, Meining A et al. 2007).

Propofol can be administered in intermittent boluses or continuous infusion (Fanti L 2004 et al., Kongkam P et al. 2008, Thaharavanich R et al. 2011). Propofol bolus administration is well documented during GI endoscopy (Hsieh Y et al. 2009, Liu S et al. 2009, Paspatis G et al. 2008, Poon C et al. 2007, Riphaus A et al. 2005, Rex D et al. 2009, Seifert H et al. 2000, Sipe B et al. 2007, Zippi M et al. 2008, Heuss L et al. 2012, Wehrmann T et al. 1999).

However, only few studies exist about the use of continuous propofol infusion in endoscopy, mainly with implementation of target-controlled infusion (TCI) (Fanti L et al. 2004, Fanti L et al. 2007, Kongkam P et al. 2008, Thaharavanich R et al. 2011, Kulling D et al. 2004, Hsu W et al. 2013). The device for propofol infusion (infusion pump) can be controlled manually (manually controlled infusion, MC) or microprocessor controlled (target-controlled infusion, TCI). In MC mode sedation provider makes each change to the infusion rate in attempt to maintain the desired level of sedation. In TCI mode all necessary changes in infusion rate are controlled by microprocessor to reach and maintain a desirable propofol plasma (C_p) or effect-site (C_e) concentration adjusted by sedation provider. Usually TCI administration protocol consider patient's age, gender and weight to predict

individual pharmacokinetic changes in propofol C_p or C_e and thus giving possibility for individualized dosing of sedatives.

Several pharmacokinetic models have been created for TCI of propofol (Marsh B et al. 1991, Schnider et al. 1999, Gepts E et al. 1987). The pharmacokinetic model described by Schnider uses C_e steering that allows achievement of desired sedation level more rapidly than with C_p steering (Leslie K et al. 2008).

In the randomized comparison between propofol bolus administration and continuous infusion for ERCP and EUS (n=100) both administration methods allowed identically good sedation with similar efficacy and patient safety. However, continuous infusion was associated with delayed recovery and more frequent hypotension (Riphaus A et al. 2012). The intermittent bolus administration of propofol is a current standard practice of propofol administration in GI endoscopy (Riphaus A et al. 2008, Vargo J et al. 2009, Heuss et al. 2012).

The use of propofol for sedation is recommended only for persons with appropriate training in administration of general anesthesia and not involved in the conduction of diagnostic or surgical procedure (Perel A 2011). Specific antagonists of propofol are not available.

5.1.3 OTHER MEDICATIONS

Ketamine

Ketamine is N-Methyl-D-aspartate receptor antagonist and produce dissociation between limbic and cortical systems with minimal respiratory and cardiovascular depressive effects (White P et al. 1982). Ketamine alone or in combination with other sedatives has been evaluated for sedation mainly in pediatric patients. In difficult-to-sedate adult patients ketamine provided deeper sedation and faster recovery than additional doses of meperidine and diazepam in patients who were inadequately sedated with the last mentioned combination during ERCP and EUS (Varadarajulu S et al. 2007). Fabbri L compared propofol-ketamine-remifentanyl sedation with propofol-remifentanyl in 322 patients during ERCP procedures. Lighter sedation levels, better analgesia, lower incidence of post-procedural nausea and vomiting and shorter discharge times were reported in patients received propofol-ketamine-remifentanyl (Fabbri L et al. 2012). A Study of Rosing showed improvement of sedation success rate (100 % vs. 85 %) in patients received midazolam/ketamine for colonoscopy compared to midazolam alone (Rosing C et al. 1991). Sedation induction with combination of ketamine, midazolam, pentazocine and propofol resulted in improved patient tolerance compared with propofol alone during ERCP (Ong WC et al. 2007).

Dexmedetomidine

Dexmedetomidine is a highly selective α -2 adrenoreceptor agonist with sedative and analgesic properties and without any significant influence on spontaneous respiration. Dexmedetomidine has approval of Food and Drug Administration for procedural sedation (Shukry M and Miller J 2010). Dexmedetomidine results in reduction of heart rate and systemic sympathetic tone without changes in baroreflex sensitivity (Hogue C et al. 2002). The role of dexmedetomidine sedation for GI endoscopy is not entirely established. The studies about dexmedetomidine suitability for GI endoscopy have controversial results. A trial investigating dexmedetomidine suitability for colonoscopy (Jalowiecki P et al. 2005) needed to be terminated because of adverse events (bradycardia and hypotension). In the study of Muller dexmedetomidine alone was less effective than propofol-fentanyl during ERCP and produced greater hemodynamic instability and prolonged recovery (Muller S et al. 2008). The studies evaluated dexmedetomidine use for upper GI endoscopies showed good results (Hashiguchi K et al. 2008, Takimoto K et al. 2011, Demiraran Y et al. 2007).

Nitrous oxide

Nitrous oxide is an odorless gas with analgesic properties and in allowed concentrations acts as a weak anesthetic. Nitrous oxide has been studied only during colonoscopy. Patient-controlled nitrous oxide inhalation showed better cardiorespiratory stability and faster recovery than midazolam/pethidine during colonoscopy (Saunders BP et al. 1994). In another study during colonoscopy nitrous oxide was less effective and produced worse intraprocedural analgesia and patient satisfaction than midazolam/meperidine (Forbes GM and Collins BJ 2000). In a study of Maslekar patient-controlled nitrous oxide inhalation (Entonox - 50 % nitrous oxide and 50 % oxygen) was compared with patient-maintained target-controlled infusion of propofol during colonoscopy in terms of analgesic efficacy, depth of sedation, manoeuvrability and patient and endoscopist satisfaction. Nitrous oxide appeared to be of equal efficacy with propofol patient-maintained target-controlled infusion during colonoscopy (Maslekar S et al. 2011). Comparison of nitrous oxide with midazolam-fentanyl sedation for colonoscopy showed better efficacy of nitrous oxide because of better pain relief and faster recovery (Maslekar S et al. 2009). The use of nitrous oxide as monosedation in GI endoscopy is not supported by sedation guidelines (Riphaus A et al. 2008).

5.1.4 SEDATION RELATED ADVERSE EVENTS

Although strict definition of sedation related adverse events (SRAE) in the existing literature lacking, in the majority of studies SRAE were defined as adverse cardiovascular or respiratory events during sedation. Despite of defined and published threshold at which an adverse event during endoscopy becomes a significant (Cotton PB et al. 2010), the designation of cardiovascular or respiratory events during sedation varies markedly in the reported studies. For example in the study of Cote' reporting the incidence of sedation-related complications during advanced Endoscopy under propofol sedation (Coté G et al. 2010) SRAE included airway modifications (chin lift, nasal airway, bag-mask ventilation, endotracheal intubation), hypoxemia (SpO₂ below 90 %), hypotension requiring vasopressors, and early procedure termination. In the retrospective study of Agostoni summarizing 8-year experience of monitored anesthesia care for GI endoscopy SRAE were defined as occurrences that warranted intervention and were classified as hypotension, desaturation, bradycardia, hypertension, arrhythmia, aspiration, respiratory depression, vomiting, cardiac arrest, respiratory arrest, angina, hypoglycemia, and/or allergic reaction (Agostoni M et al. 2011).

The most recent consensus on definition of SRAE was made by the International Sedation Task Force (ISTF) of the World Society of Intravenous Anaesthesia (World SIVA). Based on standardised definitions of SRAE the Adverse sedation event-reporting tool that is potentially relevant to all specialties and providers was created by ISTF. ISTF propose recognition of sentinel, moderate, minor and minimal SRAE (Mason K et al. 2012).

Few studies have compared traditional sedation (benzodiazepine and opioid combination) with propofol sedation during ERCP (Kongham P et al. 2008, Riphaut A et al. 2005, Vargo JJ et al. 2002, Wehrmann T et al. 1999, Jung M et al. 2000, Schilling et al. 2009). In the study of Kongham P 2008 reporting 134 ERCP patients sedated with gastroenterologist administered propofol infusion (PI) (n=67) or meperidine-midazolam (MM) boluses (n=67) SpO₂ decreased below 90 % in 20 % of patients in PI and in 30 % of patients in MM groups. Hypotension occurred in 10 % of patients in both groups and bradycardia in 3 % in PI group and in 10 % of patients in MM group. Other studies comparing propofol sedation with traditional sedation during ERCP (Riphaut A et al. 2005, Vargo JJ et al. 2002, Wehrmann T et al. 1999, Jung M et al. 2000) reported incidence of SRAE comparable with the study of Kongham. A Cochrane review concluded that there was no difference between propofol and traditional sedation regarding adverse events. Berzin T in prospective assessment of SRAE during 528 consecutive ERCP under AAS or GA reported the total incidence of SRAE 21 %: SpO₂ below 85 % occurred in 13 %, unplanned endotracheal intubation in 3 %, procedure termination in 0.2 %, hypotension in 7 %, arrhythmias in 4 % and pulmonary aspiration in 0.4 % of

patients (Berzin TM et al. 2011). In a retrospective study with 2207 ERCPs under monitored anesthesia care (Agostoni M et al. 2011) a procedural complication rate of 5.3 % and an incidence of SRAE of 0.1-3 % was found. Interestingly, in this study hypotension was reported more frequent and desaturation secondly frequent SRAE (Agostoni M et al. 2011). As a rule, monitored anesthesia care during ERCP is safe and regardless of high incidence (20-30 %) of minor SRAE major sedation related problems occurs relatively rare (5-10 %). In a retrospective data published by Wehrmann consisting of 9547 patients received propofol sedation (3151 patients propofol alone and 6396 patients combination of propofol and midazolam) for interventional upper endoscopy (EGD, n = 5374, ERCP, n = 3937, EUS, n = 236) severe SRAE, leading to interruption of the procedure were reported in 1.4 % of patients. Bag-mask ventilation was needed in 0.4 % and endotracheal intubation in 0.09 % of patients respectively. Sedation related mortality and ICU admission were reported in 0.03 % and 0.3 % of patients respectively. Emergency interventions and a higher propofol dose were assessed as an independent risk factors for cardiorespiratory complications (Wehrmann T and Riphaut A 2008).

Jowell P et al (1996) compared traditional sedation (n=31) with PCS using meperidine-midazolam mixture (n=31) during ERCP and reported that not SRAE occurred in the PCS group (Jowell P et al. 1996). In the study of Gillham about patient-maintained propofol sedation during ERCP (n=20) SRAE did not occurred but 20 % of sedations failed (Gillham M et al. 2001). In the Study of Mandel comparing midazolam-fentanyl PCS (n=24) with propofol-remifentanyl PCS (n=25) during colonoscopy SRAE were reported in 12 % of patients (Mandel J et al. 2008). Comparison of propofol-remifentanyl PCS with propofol-remifentanyl AAS during colonoscopy (Mandel J et al. 2010) reveal significant difference between study groups in the incidence of respiratory events (0 % in PCS vs. 20 % in AAS) but this study is potential for bias with AAS.

5.2 PATIENT SATISFACTION

The most important factor affecting patient satisfaction is the degree of discomfort/pain experienced by patient. Maslekar studied prospectively patient satisfaction with flexible sigmoidoscopy performed in 503 patients by medical doctors, nurses and non-medical endoscopists (non healthcare professionals) and tried to determine factors influencing patient satisfaction. No differences were detected between performing parties in patient rating for overall satisfaction. Higher pre-procedure anxiety, history of pelvic operations and higher pain scores were associated with adverse patient satisfaction (Maslekar S et al. 2010). In the study investigated influence of analgesia during flexible sigmoidoscopy patient satisfaction was significantly higher with analgesia than without (Basu S et al. 2004). In consequence,

reducing of periprocedural anxiety (sedation) and analgesia have an important role in the overall patient satisfaction. Gastroscopy under sedation is preferred by 40 % – 60 % of patients (Olithselvan A et al. 2004). Anxious female and young patients especially benefit from sedation (Rex et al. 1999, Campo R et al. 1999). The positive influence of sedation on acceptance of GI endoscopies was established in other studies (Hedenbro et al. 1991, Kinoshita Y et al. 1991, Yuno K et al. 1996, Ristikankare M et al. 1999, Marriott P et al. 2004). However, under benzodiazepine sedation patients may have discomfort or pain that the endoscopist may not notice (Rex D et al. 1999, Walmsley R and Montgomery S 1998). In comparisons of propofol with traditional sedatives during GI endoscopy propofol provided higher post-procedural patient satisfaction (Roseveare C et al. 1998, Ulmer B et al. 2003, Vargo J et al. 2002, Sipe et al. 2002, Weston B et al. 2003). In the study reported patient satisfaction under AAS during ERCP 10-point VAS sedation satisfaction score was recorded for 461 procedures. The overall mean sedation satisfaction score was somewhat higher for patients under sedation compared with patients receiving GA (9.3 vs. 8.4). Among outpatients (n=238) the mean satisfaction score was 9.9 and only 6 % of patients reported some memory of the ERCP procedure.

5.3 PATIENT-CONTROLLED SEDATION

PCS is a delivery of sedative medications during unpleasant diagnostic and therapeutic procedures that is initiated and controlled by the patient (Atkins J and Mandel J 2008). PCS is originated from patient-controlled analgesia (PCA). PCS enables the patient to control the amount of sedatives and the timing of delivery, and thus offers individual sedation for each patient and procedure. First experience of PCS clinical use was reported in dentistry (Rudkin G et al. 1991, Osborn G et al. 1991).

Patient-maintained sedation (PMS) is a modification of PCS that describes sedation which is initiated by anesthesia provider and maintained by the patient at the level desired by the patient. In the studies describing PMS sedatives were mostly administered with the use of TCI systems (Gillham M et al. 2001, Campbell L et al. 2004, Fanti L et al. 2007, Stonell C et al. 2006). There applicability of PCS and PMS has been reported in a variety of invasive procedures (Table II)

Table II Applications of PCS and PMS	
CONDITION	REFERENCE
ERCP	Jowell P 1996, Gillham M2001
colonoscopy	Mandel J 2008, Mandel J 2010, Crepeau T 2005, Roseveare C 1998, Bright E 2003, Lee D 2002, Stonell C 2006, Külling D 2001, Heuss L 2004, Ng J-M 2001, Heiman D 1998, Lee D 2004, Campbell L 2004
EUS	Agostoni M 2007
cataract surgery (supplementation to local anesthesia)	Janzen P 1999, Yun M 2008, Morley H 2002
dental treatment	Oei-Lim V 1998, Rudkin G 1991, Osborn G 1991, Chapman R 2006, Rudkin G 1992, Leitch J 2004, Rodrigo M 2003
fiberoptic bronchoscopy	Hwang J 2005,
shockwave lithotripsy	Alhashemi J 2002, Joo H 2001
dressing changes	Coimbra C 2003, Nilsson A 2008
emergency room surgical procedures	Bell A 2010
gynecology and urology	Dell R 1998, Nilsson A 2012, Tripathi M 2009, Cook L 1993
neurosurgery, orthopedics and general surgery (adjuvant to local or regional anesthesia)	Irwin M 1997, Ganapathy S 1997, Herrick I 1997, Joo J 2012, Wahlen B 2008
intensive care unit	Chlan L 2010

Sedatives used in PCS include midazolam (Jowell P et al. 1996, Rudkin G et al. 1992), propofol, or combination of both with different opioids (meperidine, fentanyl, remifentanyl, alfentanil) (Agostoni M et al. 2007, Joo H et al. 2001, Dell R and Cloote A 1998, Hwang J et al. 2005, Nilsson A et al. 2012, Crepeau T et al. 2005). Pharmacokinetics of drugs used for PCS is shown in Table III.

Table III Pharmacokinetics of drugs used for PCS			
Drug	onset of action	duration of action	t_{1/2}
midazolam	1-5 min	1-3 h	1,5 – 2.5h
propofol	30-60 sec	3-10 min	30-60 min
fentanyl	30-60 sec	30-60 min	1,5 – 3h
alfentanil	30 sec	15-20 min	1,5 – 2,5h
remifentanyl	30 sec	5-10 min	3-10 min
meperidine	1-3 min	2-3 h	4-6 h
PCS-patient-controlled sedation, t _{1/2} -biological half-life, h- hour, min-minute, sec-seconds			

Comparison between midazolam and propofol for PCS (Rudkin G et al. 1992, Mandel J et al. 2008) showed a better recovery profile after propofol PCS with comparable satisfaction with sedation and incidence of SRAE. Alfentanil and remifentanyl were not compared previously in sedative mixture for PCS.

In the majority of comparisons between PCS and anesthesia provider administered sedation, PCS leads to reduction of total dose of sedatives and faster recovery (Crepeau T et al. 2005, Roseveare C et al. 1998). In the study of Heuss comparing PCS with nurse administered propofol sedation during colonoscopy consumption of sedatives was somewhat higher in the PCS group, but significant difference between study groups was not achieved and procedures were longer in the PCS group (Heuss LT et al. 2004). PCS has been extensively studied during colonoscopy with good results (Table IV). PCS was reported to be successfully used without supervision of anesthesiologist (Table IV).

Table IV Studies about PCS for colonoscopy						
Study reference	drugs	n of patients	success rate	ASA class	SRAE	presence of anesthesiologist
Lee D 2004	propofol/ alfentanil	500	98 %	I-III	8,6 %	No
Roseveare C 1998	propofol/ alfentanil	33	100 %	I-III	0 %	Yes
Ng J-M 2001	propofol	44	100 %	I-II	0 %	Yes
Lee D 2002	propofol/ alfentanil	50 (>65y)	n/a	II-IV	4 %	No
Kulling D 2001	propofol/ alfentanil	50	100 %	I-II	4 %	No
Heuss L 2004	propofol	36	100 %	I-III	3 %	No
Crepeau T 2005	propofol	72	97 %	I-III	9 %	Yes
Mandel J 2008	propofol/ remifentanil midazolam/ fentanyl	25(PR) 25(MF)	100 %	I-III	4%(PR) 0%(MF)	Yes
Mandel J 2010	propofol/ remifentanil	25	100 %	I-II	0 %	Yes
Heiman D 1998	propofol (n=8) propofol/ alfentanil (n=12)	20	100 %	n/a	0 %	n/a
Bright E 2003	propofol/ alfentanil	33	100 %	n/a	0 %	No
n-number of patients, ASA-American Society of Anesthesiologists, SRAE-sedation related adverse events, PR-propofol/remifentanil, MF-midazolam/fentanyl, y-years, n/a-not available						

However, only 2 studies exist describing the use of PMS but not about PCS for ERCP (Jowell P 1996 et al., Gillham M et al.2001). In the study of Jowell nurse assistant administered sedation with midazolam/meperidine (n=35) was randomly compared with nurse initiated patient maintained midazolam/meperidine (n=35) sedation during ERCP. All ERCP were successfully completed. PMS failed in 3/35 patients. Patient satisfaction and incidence of SRAE did not differ between the groups (Jowell P et al. 1996). In a pilot study of Gillham PMS with propofol TCI described in 20 ERCP patients. PMS failed in 4/20 patients. Patient and endoscopist satisfaction was high and serious SRAE did not occur (Gillham M et al. 2001).

5.4 ASSESSMENT OF SEDATION

Monitoring of sedation levels during GI sedation is recommended in the recent sedation guideline (Cohen L et al. 2010). However, assessment of sedation level remains to be an elusive aim. A number of sedation scales which measure the patient's responsiveness to verbal, physical or painful stimuli (Ramsay M et al. 1974, Manyam S et al. 2007, Gillham M et al. 2001, Ely E et al. 2003, Chernic D et al. 1990) were developed predominantly for the measurement of unconsciousness. Although sedation scales often used in the assessment of procedural sedation, none of them has been validated in GI sedation. For example with the aid of MOAA/S scale differentiation between deep sedation and general anesthesia may be cumbersome because of the lack of sensitivity (Bailey P and Zuccaro G 2006).

Level of sedation may be quantified by processed electroencephalography. This type of monitors includes bispectral index and state entropy. The results of studies about utility of bispectral index and state entropy monitoring in sedated patients are controversial (Mahon P et al. 2008, Drake L et al. 2006, Sasaki T et al. 2012, von Delius V et al. 2012) and do not support its routine use in GI sedation. Finally, auditory evoked potentials have been investigated in the assessment of sedation in volunteers with promising effects (Haenggi M et al. 2004) but studies are lacking in GI sedation.

6 AIMS OF THE STUDY

The aim of this thesis was to examine the suitability of PCS for the sedation of patients undergoing ERCP in terms of propofol consumption, sedation levels, sedation related adverse events, patient satisfaction with sedation, the ease of ERCP performance, and recovery profile. The specific aims of the studies I-IV were:

- 1) To compare PCS with anesthesiologist administered propofol sedation during ERCP using either a constant infusion or TCI (I, III)
- 2) To compare remifentanyl and alfentanil in PCS during ERCP (II)
- 4) To evaluate the suitability of dexmedetomidine in addition to PCS for sedation of alcoholics during ERCP (IV)
- 4) To assess the success rate of PCS during ERCP (I-IV)

7 MATERIALS AND METHODS

7.1 PATIENTS

The thesis population consisted of 293 patients undergoing elective ERCP in the Endoscopy unit at Helsinki University Central Hospital from January 2009 to January 2011 (studies I-IV). Demographics of the study patients are shown in the Table 1. Among study patients 101(35 %) were females and 192(65 %) males. 201 (69 %) patients belonged to ASA class I and II and 92(31 %) patients to ASA class III.

<i>Demographics and co-morbidities</i>	I	II	III	IV
patients, n	80	81	82	50
Age (mean, (SD))	51(12)	48(12)	47(12)	50(8)
Gender (M/F) (n)	51/29	46/35	53/29	42/8
BMI (mean, (SD))	25(5)	25(5)	23(4)	23(4)
ASA class 1/2/3 (n)	13/37/30	25/32/24	28/31/23	7/28/15
Cardiovascular disease % (n)	28(22)	27(22)	26(21)	22(11)
Diabetes % (n)	20(16)	15(12)	16(13)	14(7)
Chronic lung disease % (n)	3(2)	10(8)	5(4)	6(3)
n-number of patients, SD-standard deviation, M-male, F-female, BMI-body mass index, ASA-American Society of Anesthesiology				

7.2 STUDY DESIGNS

All studies I-IV were prospective randomized controlled trials with parallel assignment (Table 2). Sealed non-transparent envelopes were used for randomization in studies I-IV. Computer-generated random numbers were used in the study IV and letters in the studies I-III. Informed content was obtained on the day of procedure thereafter patients were allocated to the study arm.

Table 2 Design of the studies				
	I	II	III	IV
Date of enrolment	Jan-Apr 2009	June-Sep 2009	Mar-Nov 2010	Mar2010-Jan-11
Number of Arms	2	3	2	2
Masking	open label	double-blind	open label	double-blind
Inclusion Criteria	elective ERCP-patients age 18-70 years	elective ERCP-patients age 18-70 years	elective ERCP-patients age 18-75 years	elective ERCP-patients with chronic alcohol pancreatitis age 18-65 years
Exclusion Criteria	Allergy to propofol or opioid, ASA-class greater than 3, inability to co-operate, drugs abuse	Allergy to propofol or opioid, drug addiction, inability to co-operate, ASA class greater than 3, patient's refusal	Allergy to propofol or opioid; inability to cooperate; ASA-class greater than 3	Allergy to dexmedetomidine, propofol or any opioid, ASA-class greater when 3
<i>Registration/approval numbers</i>				
NCT	NCT01079312	NCT01350037	NCT01070680	NCT01072435
Eudra CT	2008-007968-42	2009-012398-36	2009-014862-25	2009-015564-34
Ethics committee	429/13/03/02/08	116/13/03/02/09	249/13/03/02/2009	287/13/03/02/2009

7.3 ERCP

All patients (studies I-IV) were fasted at least 6 hours before ERCP. Levofloxacin was given orally for antibiotic prophylaxis, other premedication was not used. Patients were placed into the prone position. Procedures were performed with the use of duodenoscope (Olympus TJF-160VR) by one of the five senior endoscopists. Intestinal lumen was insufflated with air in all studies (I-IV). At the end of ERCP endoscopists evaluated ERCP degree of difficulty and ease of performance with the use of structured questionnaire (Chutkan RK et al. 2006, Gillham M et al. 2001).

7.4 ADMINISTRATION OF SEDATION

After placement of intravenous cannula infusion of Ringer-acetate was started at the rate of 300 ml · h⁻¹. All patients received glycopyrrolate 0.2 mg and lidocaine 20mg intravenously five minutes before the start of procedure. Lidocaine 10 mg · ml⁻¹ was sprayed into the pharynx to achieve pharyngeal anesthesia. Supplemental oxygen was administered to all patients at rate 4 l · min⁻¹. All procedures were performed under sedation with maintained spontaneous respiration and unprotected airways as follows.

7.4.1 PATIENT-CONTROLLED SEDATION

Self-administration of propofol or propofol and opioid mixture (PCS) was used by the patients in all studies (I-IV). A syringe pump connected with administration button (Syramed μ SP6000™, Arcomed AG, Regensdorf, Switzerland) was programmed to deliver 1 ml single bolus dose. Lockout time was adjusted to “zero”, dose-limitation and background infusion were not used. Sedative mixtures were prepared immediately before the procedure (Table 3).

	I	II		III	IV	
propofol 10 mg · ml ⁻¹ , ml	20	20	20	20	50	40
alfentanil 0.5 mg · ml ⁻¹ , ml	-	2	-	4	-	6
remifentanil 0.05 mg · ml ⁻¹ , ml	5	-	5	-	-	-
NaCl 0.9 mg · ml ⁻¹ , ml	-	3	-	1	-	4

Patients were instructed to use self-administration device every time when they would feel pain or discomfort or wanted to be more deeply sedated. The patients were advised to take few doses for the induction of sedation before the start of ERCP. Patients were asked to take 1-2 additional doses if nociceptive stimulus (e.g. dilatation of biliar or pancreatic tract) was anticipated during the procedure. If patient became restless, lost co-operation and markedly affect procedure performance, propofol boluses 20-30 mg were administered by the anesthesiologist and, if needed, infusion of propofol was started. PCS was considered as failed if any propofol was administered by the anesthesiologist in patients using PCS.

7.4.2 ANESTHESIOLOGIST ADMINISTERED SEDATION

In studies I and III sedation was managed by anesthesiologist in control groups. In study I sedation was initiated with propofol 40 mg and fentanyl 0.05 mg boluses and maintained with propofol infusion at the rate of 0.5 - 9 mg · kg⁻¹ · h⁻¹. If needed, propofol 20 - 40 mg and/or fentanyl 0.05 mg boluses were given during the procedure.

In study III propofol was administered with the use of TCI. ERCP was started after achievement of effect-site concentration (C_E) 2 mcg · ml⁻¹ using Schnider pharmacokinetic model. C_E was adjusted with increments of 0.5 mcg · ml⁻¹ in order to avoid deep sedation. Alfentanil (0.5 mg) bolus was given if signs of inadequate analgesia (grimace, increase of more than 30 % in the heart rate, patient's request) occurred during therapeutic intervention (e.g. stricture dilatation).

7.4.3 DEXMEDETOMIDINE INFUSION

In study IV patients from the intervention group received dexmedetomidine infusion. Loading dose $1 \text{ mcg} \cdot \text{kg}^{-1}$ was infused in 10 minutes before start of ERCP. Thereafter maintenance infusion at the constant rate of $0.7 \text{ mcg} \cdot \text{kg}^{-1}$ was used until the end of procedure. Patients from control group received placebo at the same rate.

7.5 MEASUREMENTS

After arrival to the procedural room standard monitoring for deep sedation was applied: continuous ECG, HR, NIBP at five minute interval, and SpO_2 . Additionally partial pressure of EtCO_2 via nasal cannula and sedation levels were monitored. Sedation levels were defined and registered at five minute interval with the use of MOAA/S, Ramsay, Gillham and Richmond Agitation-Sedation scales (Table 4).

7.5.1 PRIMARY OUTCOME MEASURE

In all studies consumption of propofol (mg) was the primary outcome measure. At the end of ERCP administration of all sedative drugs was discontinued and total amount of propofol, received by the patients, was calculated.

7.5.2 SECONDARY OUTCOME MEASURES

Cardiorespiratory values, sedation levels, the incidence of SRAE (see below), success rate of PCS (see below), opioid consumption, difficulty of procedure performance, patient satisfaction with sedation, quickness of the recovery, intensity of post-procedural pain, and occurrence of nausea were considered as secondary outcome measures in all studies. Additionally, dexmedetomidine consumption was the secondary outcome measure in the study IV.

Desaturation ($\text{SpO}_2 < 90 \%$), pulmonary aspiration, respiratory depression (respiratory rate $\leq 6 \cdot \text{min}^{-1}$), hypotension (systolic blood pressure $< 90 \text{ mmHg}$), and arrhythmia were identified as possible SRAE. Sedation was considered as successful if ERCP was not interrupted due to sedation related complication and/or propofol was not administered by an anesthesiologist for patients used PCS. Following classification (Chutkan RK et al. 2006) was used by endoscopists for evaluation of degree of difficulty of ERCP: Grade 1: diagnostic cholangiogram or pancreatogram, biliary or pancreatic brush cytology, standard sphincterotomy, removal of $< 10 \text{ mm}$ stones, stricture dilatation/stent for extrahepatic stricture or bile leak; Grade 2: removal of $> 10 \text{ mm}$ common bile duct stones, stricture dilatation/stent for hilar tumors or benign intrahepatic strictures, diagnostic cholangiogram or

pancreatogram with BII anatomy, minor papilla cannulation; Grade 3: any therapy to biliary duct with BII anatomy, removal of intrahepatic stones or any stones with lithotripsy, all pancreatic therapy. Sedation levels were evaluated with the use of sedation scales (Table 4). Intensity of post-procedural pain was measured with verbal rating scale: 0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain. A seven-step numeric range Likert scale (1 = awfully unsatisfied, 2 = unsatisfied, 3 = almost unsatisfied, 4 = I don't know, 5 = almost satisfied, 6 = satisfied, 7 = awfully satisfied) was applied for measurement of patient's satisfaction with sedation. Also patients were asked about their preference for received sedation in case of new ERCP. Quickness of the recovery was evaluated with Aldrete scale (Aldrete JA 1995).

Table 4 Sedation scores used in the studies I-IV		
Response		Score
Ramsay sedation score (Ramsay M et al. 1974)		
Patient paralyzed, unable to assess level of sedation		0
Patient anxious, agitated, or restless		1
Patient co-operative, oriented, and tranquil		2
Patient sedated but responds to commands		3
Patient asleep but responds to glabellar tap		4
Patient asleep, responds to nail bed pressure		5
Patient asleep, no response to nail bed pressure		6
Gillham sedation score (Gillham M et al. 2001)		
Awake and anxious		1
Awake not anxious		2
Speech slurred		3
Eyes closed, responds to speech		4
Eyes closed, responds to shaking		5
Unresponsive		6
MOAA/S (Manyam S et al. 2007)		
Responds readily to name spoken in normal tone		5
Lethargic response to name spoken in normal tone		4
Responds only after name is called loudly and/or repeatedly		3
Responds only after mild prodding or shaking		2
Does not respond to mild prodding or shaking		1
Does not respond to noxious stimulus		0
Richmond Agitation-Sedation Scale (RASS) (Ely EW et al. 2007)		
Description	Term	score
Overtly combative, violent, immediate danger to staff	Combative	+4
Pulls or removes tube(s), catheter(s); aggressive	Very agitated	+3
Frequent nonpurposeful movements, fights ventilator	Agitated	+2
Anxious but movements not aggressive or vigorous	Restless	+1
Alert and calm		0
Not fully alert, but has sustained awakening (eye opening to voice >10 sec.)	Drowsy	-1
Briefly awakens with eye contact to voice <10 sec	Light sedation	-2
Movement or eye opening to voice (but no eye contact)	Moderate sedation	-3
No response to voice, but movement or eye opening to physical stimulation	Deep sedation	-4
No response to voice or physical stimulation	Unarousable	-5

7.5.3 PROPOFOL PLASMA CONCENTRATIONS

In study I blood samples were obtained randomly from ten patients in both groups before ERCP began, after papilla cannulation and at the end of ERCP. Obtained blood samples were stored in ice thereafter plasma was separated and frozen. Propofol concentrations were determined by high-performance liquid chromatography with fluorescence detection in the Laboratory of the Department of Clinical Pharmacology, Helsinki University Central Hospital, Meilahti (Plummer G 1987). The detection limit of the assay was $0.5 \text{ mcg} \cdot \text{l}^{-1}$ and the day-to-day CV 2.83-8.13 %.

7.6 STATISTICAL ANALYSIS

Sample sizes were calculated to achieve statistical power of 80 % ($\alpha=0.05$, $SD=85 \text{ mg}$) to detect 100 mg (study I) or 70 mg (studies II-IV) difference in the consumption of propofol between the groups. Possible incomplete studies due to sedation adverse events and cancellations were considered in the sample size calculation.

Normality of data distribution was tested with Kolmogorov-Smirnov test. Continuous normally distributed data were compared with a two-tailed t-test and data with abnormal distribution with Mann-Whitney U-test. A general linear modeling for repeated measures was used to detect statistical differences in cardiorespiratory values and sedation scores between the groups. Differences in categorical variables were tested with Fisher's exact test or with Fisher-Freeman-Halton test. Bonferroni correction was used in multiple comparisons (study III) by adjusting the local significance level from $P < 0.05$ to $P < 0.025$ i.e. maximum two comparisons. Two-sided P-values are used. All statistics in studies II and II were performed with PASW 18 (SPSS Inc.) and IBM SPSS (v20, IBM Corporation, New York, NY)

7.7 ETHICAL CONSIDERATIONS

All Studies were conducted according to the revised Declaration of Helsinki (WMA 2008), and were approved by by the Institutional Ethics committee of Helsinki University Central Hospital and The Finnish National Agency for Medicines. All patients gave their written informed consent before entering the studies.

8 RESULTS

PERFORMED ERCP

ERCP was performed for all patients as planned. Performed ERCP characteristics are shown in the Table R1.

Table R1 Performed ERCP				
	I	II	III	IV
ERCP duration, min mean (SD)	24(13)	25(14)	24(13)	24(13)
Degree of difficulty 1 / 2 / 3 (Chutkan RK et al. 2006)	46 / 3 / 33	53 / 7 / 21	53 / 10 / 16	7 / 1 / 42
ERC, common bile duct stone extraction (n)	6	20	12	3
Biliary/pancreatic stent placement/exchange/removal (n)	46	37	28	38
Biliary/ pancreatic sphincterotomy (n)	40	52	36	20
Pneumatic dilatation of biliary/ pancreatic duct (n)	20	25	11	23

The ease of ERCP performance did not differ between the study groups (Table R2). Two procedural complications occurred: blood vessel perforation with guide wire and duodenum perforation. Both of these cases were treated conservatively and had uneventful recovery. ERCP was interrupted in one patient for sedation reason (marked breathing depression in patient sedated with propofol-remifentanyl PCS (I)).

Table R2 The ease of ERCP performance, mean (SD)									
Study	I		II			III		IV	
Study arm	PCS	PI	R	A1	A2	PCS	TCI	DEX	PLC
The ease of ERCP perform. (mean (SD))	8.0 (2.4)	7.8 (2.8)	7.9 (1.7)	8.8 (2.5)	8.0 (2.3)	8.5(2.3)	9.3(3.0)	8.8 (2.7)	8.2 (2.2)

CONSUMPTION OF PROPOFOL

The consumption of propofol was significantly different between study groups in studies I, III, IV and did not differ significantly in study II (Table R3).

Table R3 Propofol consumption (mg) during ERCP, mean (SD)

Study	I		II			III		IV	
Study arm	PCS	PI	R	A1	A2	PCS	TCI	DEX	PLC
Propofol consumption, mg mean (SD)	175 (98)	249 (138)	177(105)	197 (88)	162 (70)	224(101)	306(124)	116 (61)	159 (72)

CONSUMPTION OF OPIOID

In the studies I-III opioid consumption did not differ significantly between the groups (table R4). Significant (P=0.008) difference in alfentanil consumption was founded between dexmedetomidine and placebo groups in study IV. The mean difference between the groups was 0.43 mg (95 % CI; 0.1- 0.6 mg).

Table R4 Consumption of opioid , mean(SD)

Study	Study arm	fentanyl	alfentanil	remifentanil
I	PCS	----	----	0.2 (0.1) mg
	PI	0.1 (0.03) mg	----	----
II	R	----	----	0.05 (0.03) mg
	A1	----	1.1 (0.5) mg	----
	A2	----	1.5 (0.8) mg	----
III	PCS	----	0.5(0.4) mg	----
	TCI	----	0.5(0.4) mg	----
IV	Dex	----	0.8 (0.4) mg*	----
	Placebo	----	1.2 (0.6) mg	----

PI-propofol infusion, R-remifentanil 0.01 mg·ml⁻¹, A1- alfentanil 0.04 mg·ml⁻¹, A2 - alfentanil 0.08 mg·ml⁻¹, Dex-dexmedetomidine, *significant difference in alfentanil consumption between dexmedetomidine and placebo groups, P=0.008

PCS SUCCESS RATE

The mean (SD) success rate of PCS in all studies was 92(3) %. Detailed success rate of PCS is shown in the Table R5.

Table R5 PCS success rate

Study	I	II			III	IV	
Study arm	PCS	R	A1	A2	PCS	DEX	PLC
success rate of PCS among study arms,%(n)	93 % (38/41)	89% (24/27)	93% (25/27)	93% (25/27)	93 % (38/41)	76 % (19/25)	100% (25/25)
average success rate, mean (SD)% (n)	95 % (38/40)	92(2) % (74/81)			93 % (38/41)	88(17) % (44/50)	

Among the failed PCS cases 12 patients received additional propofol boluses and in 5 patients sedation was converted to the anesthesiologist-managed propofol infusion and in one case ERCP was interrupted because of the respiratory depression.

SEDATION LEVELS

In the study I sedation levels were significantly ($P < 0.0001$) lighter in patients receiving PCS than in control group (propofol infusion) (Fig 1A). In the study II sedation levels during ERCP did not differ significantly between the study groups (Fig 1B). In the study III sedation levels were significantly deeper in the group receiving propofol TCI at 10, 15, 20, and 25 minutes intraprocedurally, $P = 0.002 - 0.035$ (Fig 1C). In the study IV sedation levels were significantly deeper in patients receiving dexmedetomidine than in control (placebo) group, $P = 0.021 - 0.032$ (Fig 1D).

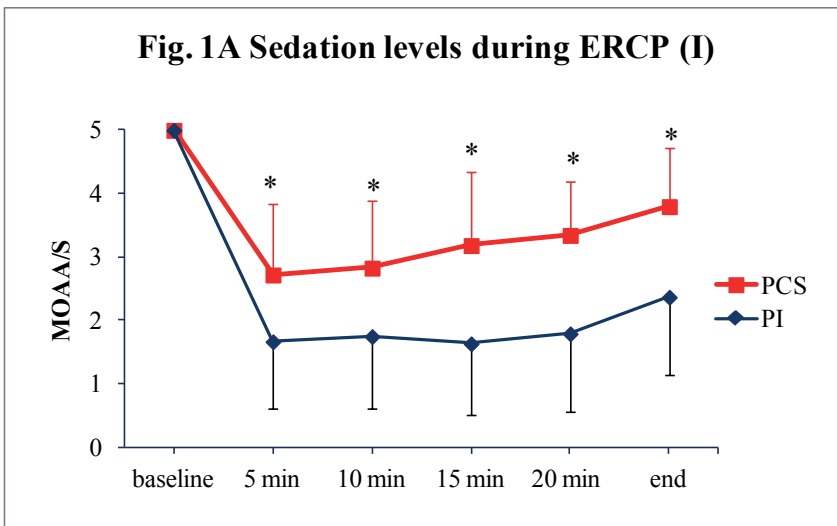


Figure 1A. Sedation levels during ERCP(I). *Significant difference observed between PCS and PI at 5,10,15,20 minutes intraprocedurally and at the end of ERCP, $P < 0.0001$. PCS-patient-controlled sedation, PI-propofol infusion. MOAA/S - Modified Observer's Assessment of Alertness and Sedation: 5-Responds readily to name spoken in normal tone, 4-Lethargic response to name spoken in normal tone, 3-Responds only after name is called loudly and/or repeatedly, 2-Responds only after mild prodding or shaking, 1-Does not respond to mild prodding or shaking, 0-Does not respond to noxious stimulus.

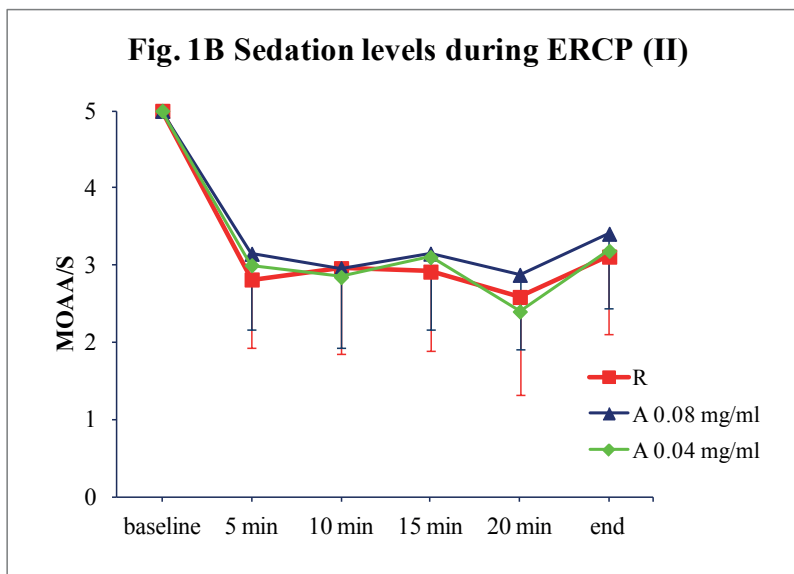


Figure 1B. Sedation levels during ERCP(II). R-remifentanyl 0.01 mg · ml⁻¹; A 0.04 mg/ml-alfentanil 0.04 mg · ml⁻¹; A 0.08 mg/ml-alfentanil 0.08 mg · ml⁻¹; MOAA/S - Modified Observer's Assessment of Alertness and Sedation: 5-Responds readily to name spoken in normal tone, 4-Lethargic response to name spoken in normal tone, 3-Responds only after name is called loudly and/or repeatedly, 2-Responds only after mild prodding or shaking, 1-Does not respond to mild prodding or shaking, 0-Does not respond to noxious stimulus.

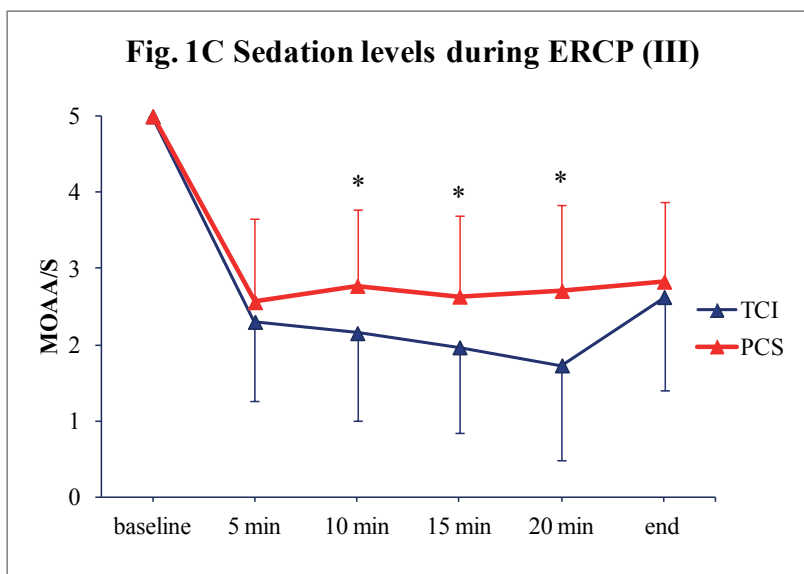


Figure 1C. Sedation levels during ERCP(III). *Significant difference observed between PCS and TCI groups at 10,15,20 minutes intraprocedurally, $P < 0.05$. PCS-patient-controlled sedation, TCI-target-controlled infusion, MOAA/S - Modified Observer's Assessment of Alertness and Sedation: 5-Responds readily to name spoken in normal tone, 4-Lethargic response to name spoken in normal tone, 3-Responds only after name is called loudly and/or repeatedly, 2-Responds only after mild prodding or shaking, 1-Does not respond to mild prodding or shaking, 0-Does not respond to noxious stimulus.

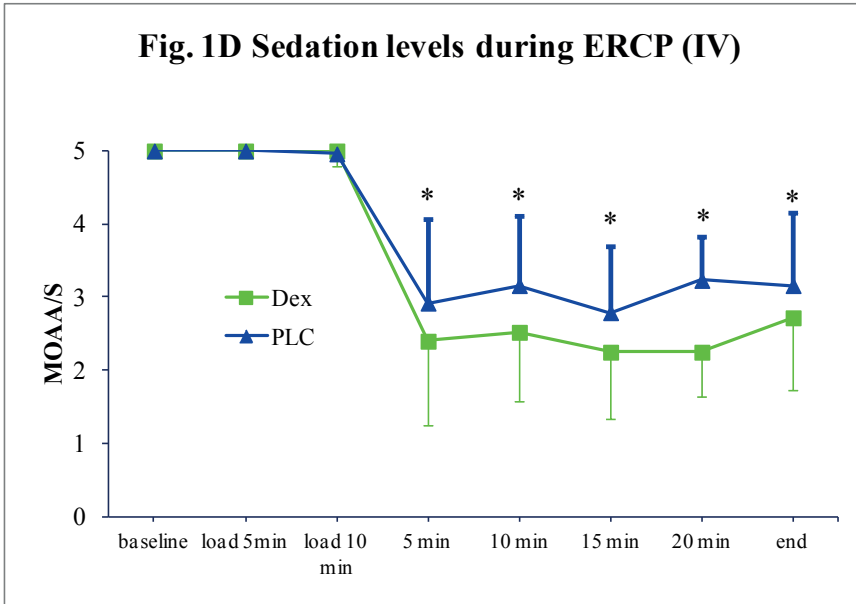


Figure 1D. Sedation levels during ERCP(IV). *Significant difference observed between PLC and Dex groups at 5,10,15,20 minutes intraprocedurally and at the end of ERCP, $P < 0.05$. PLC-placebo, Dex-dexmedetomidine, MOAA/S - Modified Observer's Assessment of Alertness and Sedation: 5-Responds readily to name spoken in normal tone, 4-Lethargic response to name spoken in normal tone, 3-Responds only after name is called loudly and/or repeatedly, 2-Responds only after mild prodding or shaking, 1-Does not respond to mild prodding or shaking, 0-Does not respond to noxious stimulus.

VITAL SIGNS

In the study I mean respiratory rate was significantly higher in patients receiving propofol infusion than in patients receiving PCS, $P < 0.05$. In the study II significant difference in the mean respiratory rate ($P = 0.006$) and in the mean arterial pressure ($P = 0.0247$) was observed between patients receiving remifentanyl and alfentanil in concentration $0.04 \text{ mg} \cdot \text{ml}^{-1}$. In the study IV mean heart rate was significantly higher in the group receiving placebo ($P < 0.001$). Other marked differences in vital signs were not founded between the study groups (Figures 2 A-D, 3A-D, 4 A-D, 5 A-D).

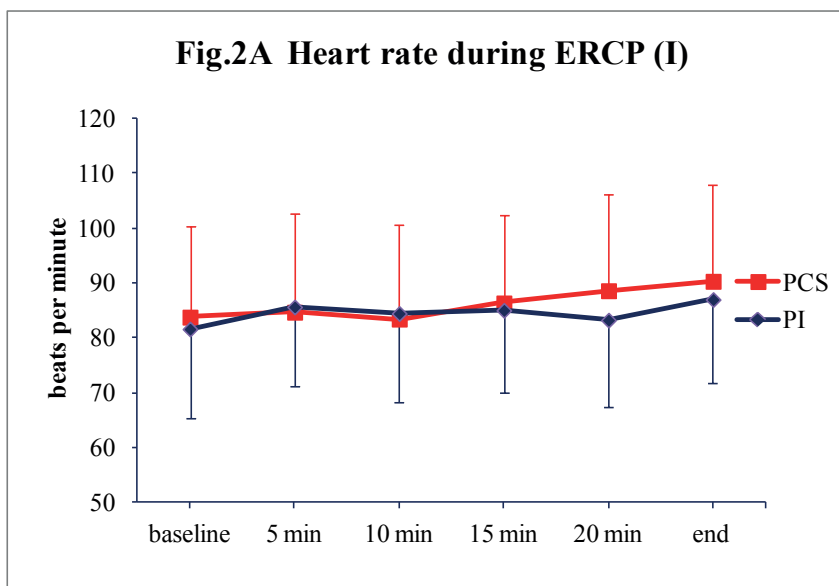


Figure 2A. Heart rate during ERCP(I). PCS-patient-controlled sedation, PI-propofol infusion.

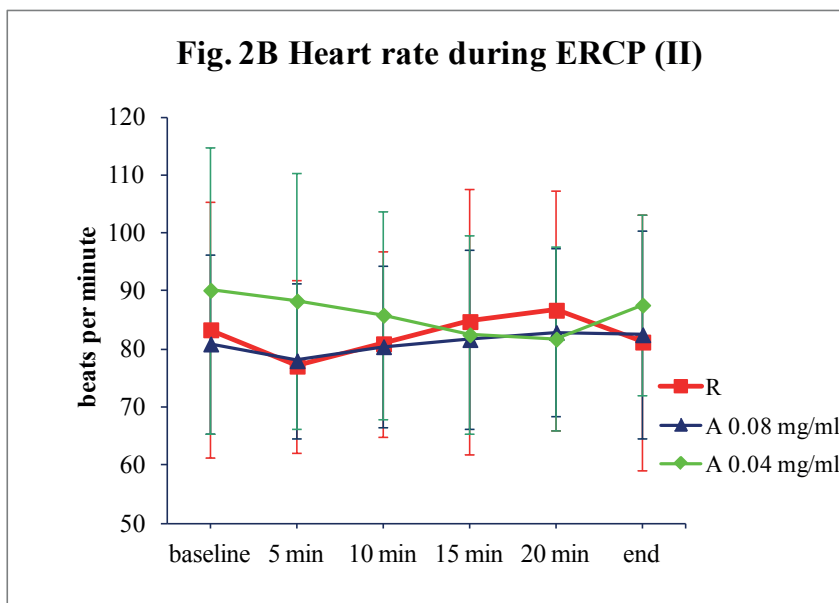


Figure 2B. Heart rate during ERCP(II). R-remifentanyl $0.01 \text{ mg} \cdot \text{ml}^{-1}$; A 0.04 mg/ml -alfentanil $0.04 \text{ mg} \cdot \text{ml}^{-1}$; A 0.08 mg/ml -alfentanil $0.08 \text{ mg} \cdot \text{ml}^{-1}$.

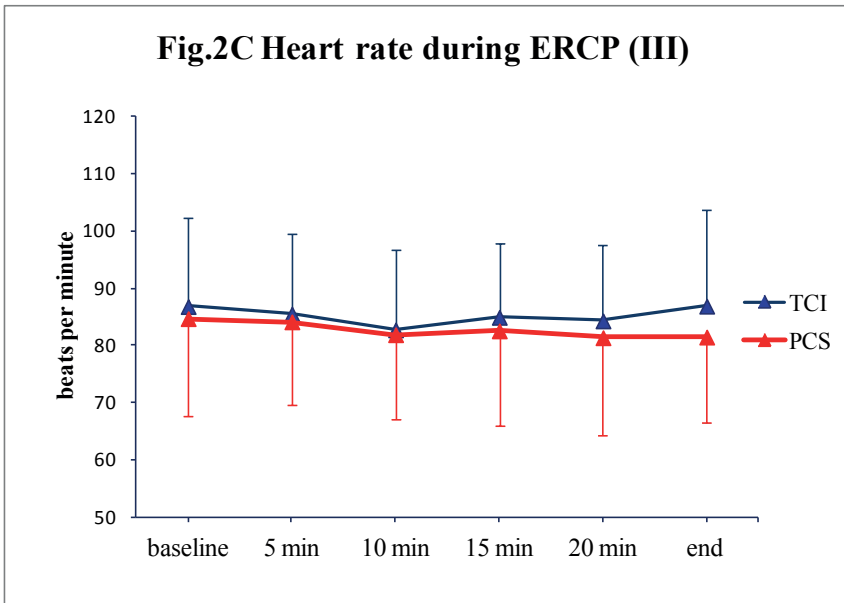


Figure 2C. Heart rate during ERCP(III). PCS-patient-controlled sedation, TCI-target-controlled infusion.

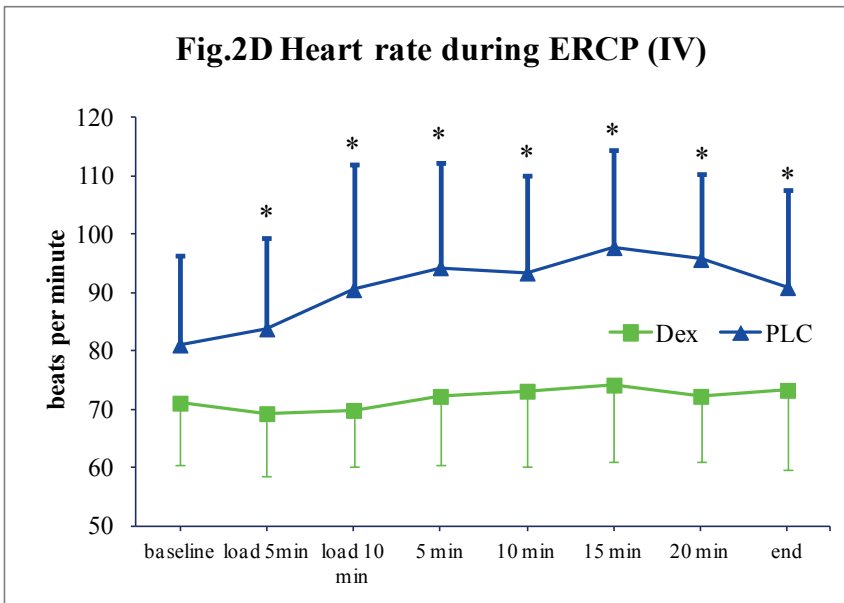


Figure 2D. Heart rate during ERCP(IV). *Significant difference observed between PLC and Dex groups during the procedure, $P < 0.05$. PLC-placebo, Dex-dexmedetomidine.

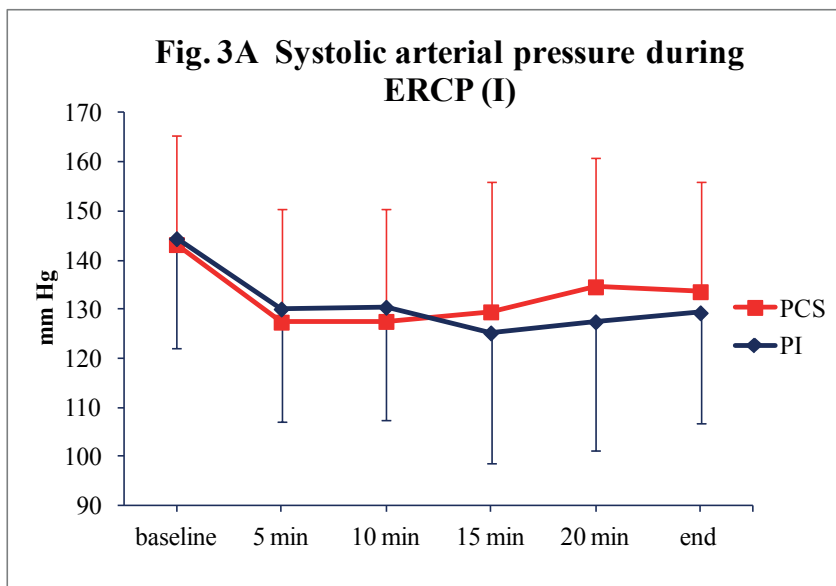


Figure 3A. Systolic arterial pressure during ERCP(I). PCS-patient-controlled sedation, PI-propofol infusion.

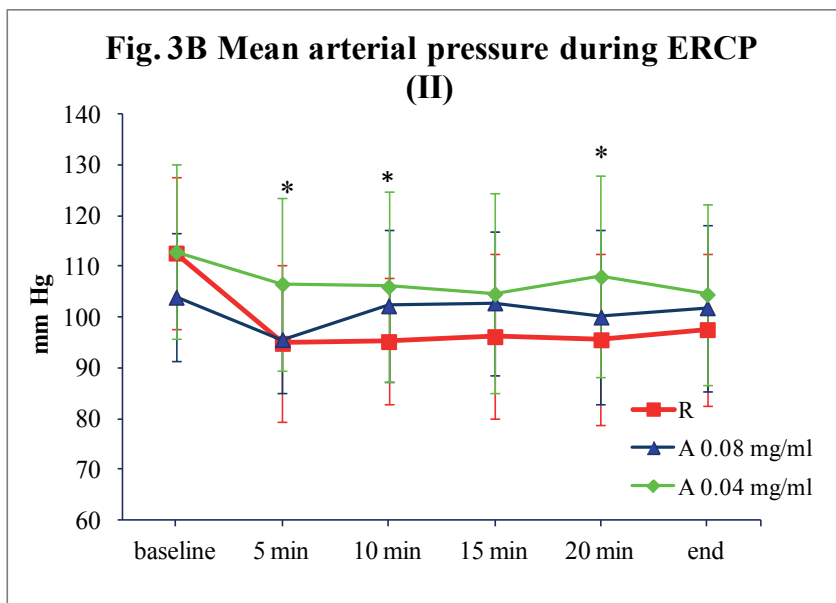


Figure 3B. Mean arterial pressure during ERCP(II). *Significant difference observed between R and A 0.04 mg/ml at 5,10,20 minutes intraprocedurally, $P < 0.05$. R-remifentanyl 0.01 mg · ml⁻¹; A 0.04 mg/ml-alfentanil 0.04 mg · ml⁻¹; A 0.08 mg/ml-alfentanil 0.08 mg · ml⁻¹.

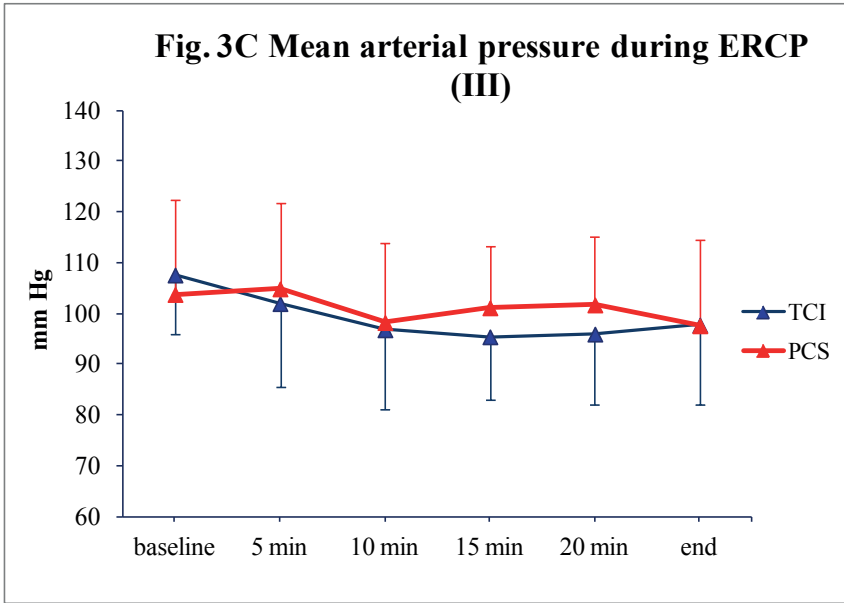


Figure 3C. Mean arterial pressure during ERCP(III). PCS-patient-controlled sedation, TCI-target-controlled infusion.

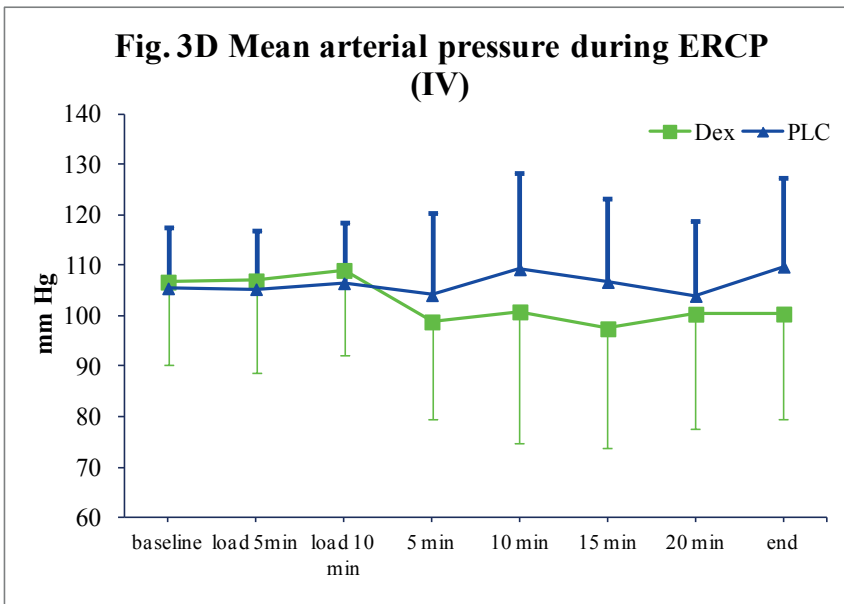


Figure 3D. Mean arterial pressure during ERCP(IV). PLC-placebo, Dex-dexmedetomidine.

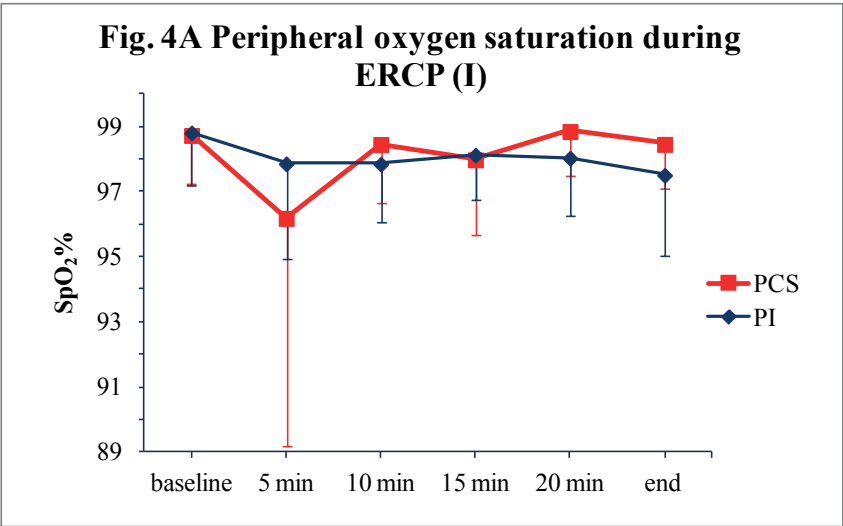


Figure 4A. Peripheral oxygen saturation during ERCP(I). PCS-patient-controlled sedation, PI-propofol infusion.

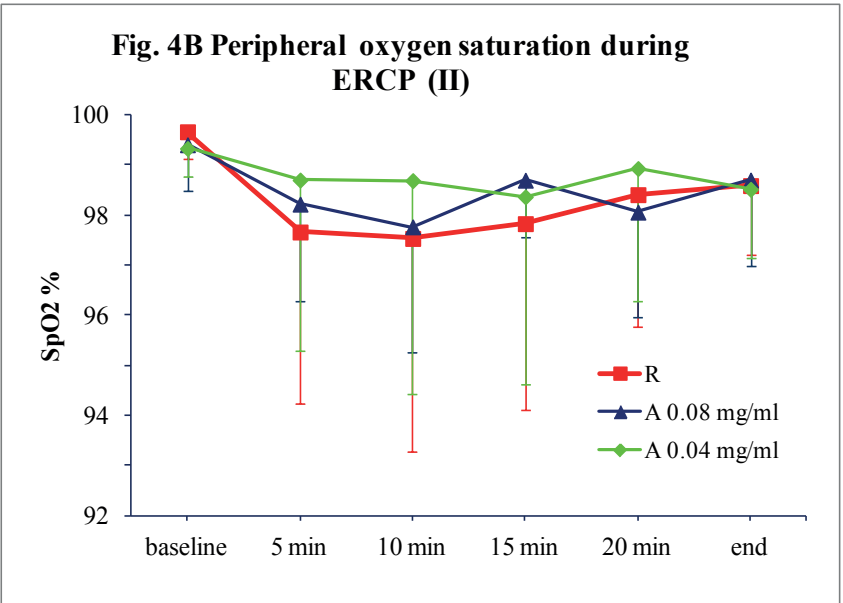


Figure 4B. Peripheral oxygen saturation during ERCP(II). R-remifentanyl 0.01 mg · ml⁻¹; A 0.04 mg/ml-alfentanil 0.04 mg · ml⁻¹; A 0.08 mg/ml-alfentanil 0.08 mg · ml⁻¹.

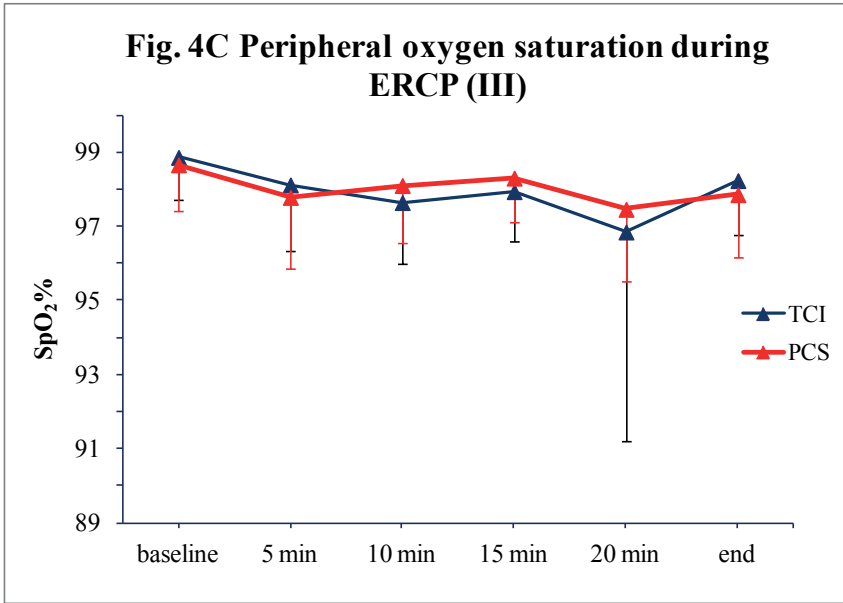


Figure 4C. Peripheral oxygen saturation during ERCP(III). PCS-patient-controlled sedation, TCI-target-controlled infusion.

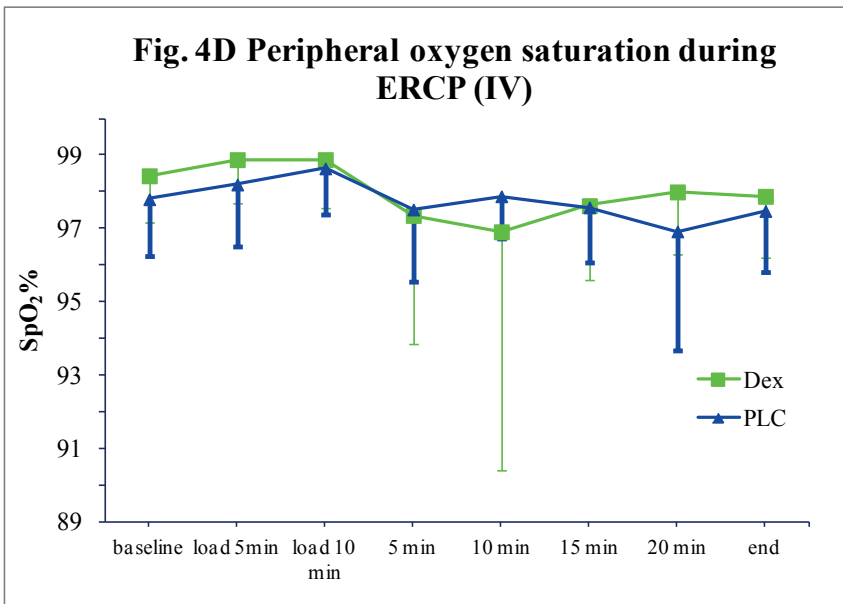


Figure 4D. Peripheral oxygen saturation during ERCP(IV). PLC-placebo, Dex-dexmedetomidine.

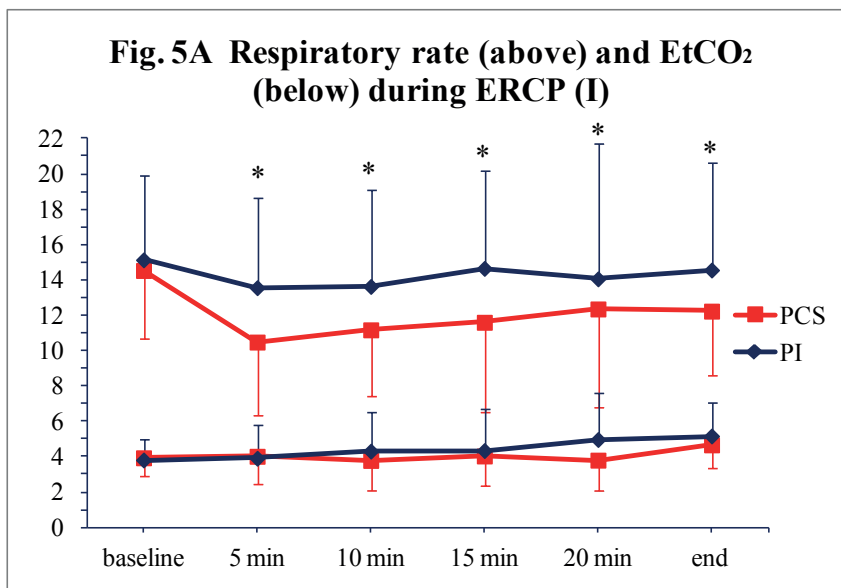


Figure 5A. Respiratory rate and partial end-tidal carbon dioxide concentration during ERCP (I). *Significant difference observed between PCS and PI intraprocedurally and at the end of ERCP, $P < 0.05$. PCS-patient-controlled sedation, PI-propofol infusion.

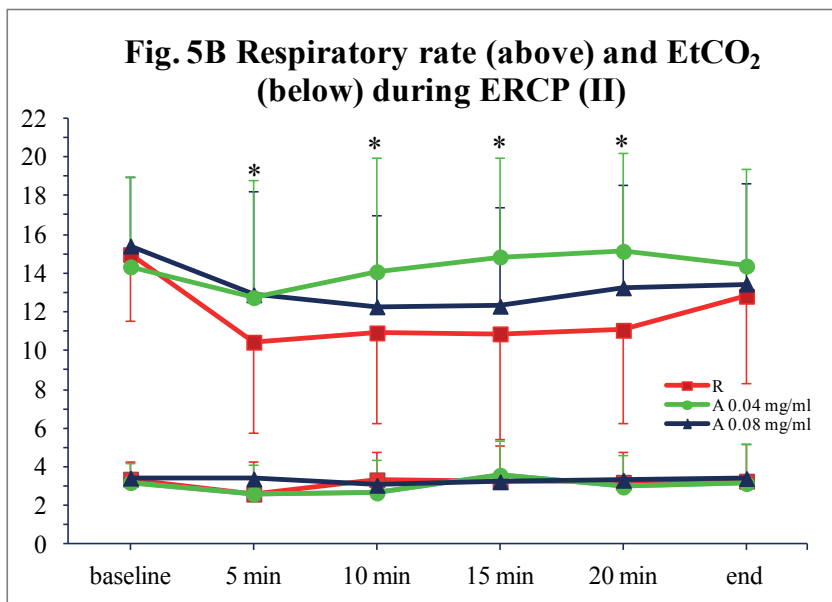


Figure 5B. Respiratory rate and partial end-tidal carbon dioxide concentration during ERCP(II). *Significant difference observed between R and A 0.04 mg/ml at 5,10,15,20 minutes intraprocedurally, $P < 0.05$. R-remifentanil 0.01 mg · ml⁻¹; A 0.04 mg/ml-alfentanil 0.04 mg · ml⁻¹; A 0.08 mg/ml-alfentanil 0.08 mg · ml⁻¹.

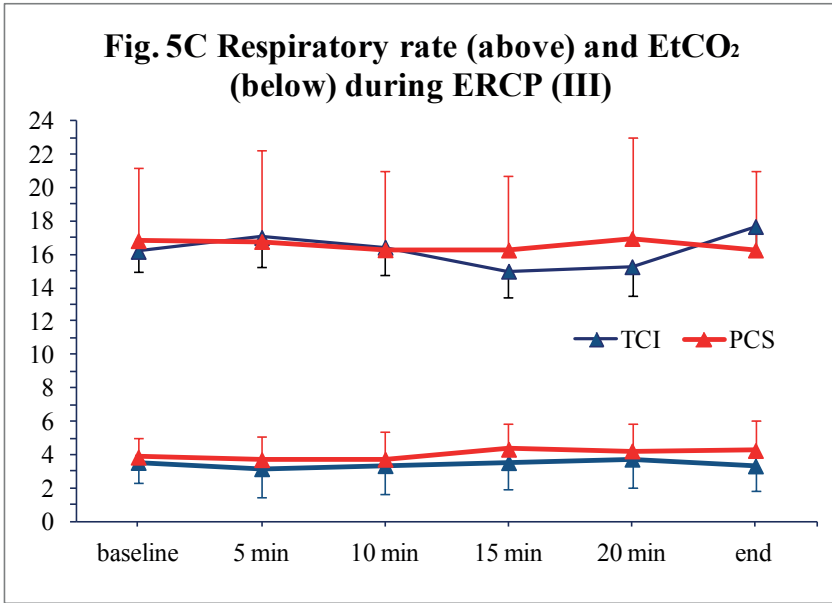


Figure 5C. Respiratory rate and partial end-tidal carbon dioxide concentration during ERCP(III). PCS-patient-controlled sedation, TCI-target-controlled infusion.

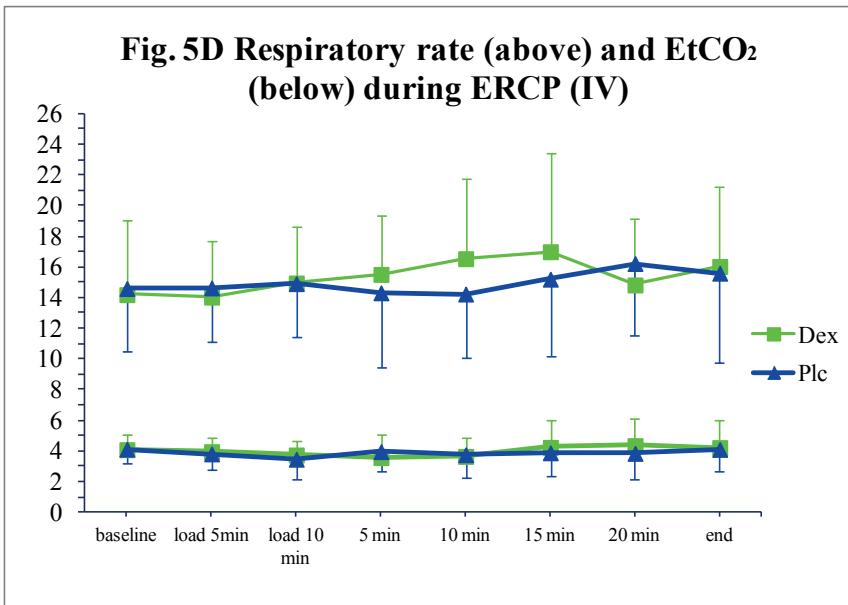


Figure 5D. Respiratory rate and partial end-tidal carbon dioxide concentration during ERCP(IV). PLC-placebo, Dex-dexmedetomidine.

SRAE (PCS)

212 patients were sedated with the use of PCS in the studies I-IV. Severe respiratory depression requiring procedure interruption and bag-mask ventilation occurred in one (0.5 %) patient sedated with propofol-remifentanyl PCS (I). Desaturations and mild respiratory depression were observed in 26(12 %) of patients. All desaturations were treated with oxygen flow increase to $8 \text{ l} \cdot \text{min}^{-1}$. Additionally nasal airway and chin lift manoeuvre were used each in four patients. Tracheal intubation was not needed for any patient. Severe hypotension occurred in one patient sedated with combination of PCS and dexmedetomidine. Oversedation (MOAA/S=1) was observed in 96(45 %) patients. The incidence of SRAE did not differ significantly between patients receiving PCS and control groups (AAS). In the study III all sedation related adverse events were associated with combination of propofol and alfentanil ($P=0.03$). Arrhythmia and pulmonary aspiration were not observed.

SRAE (CONTROL GROUPS)

In control groups sedation was administered by the anesthesiologist for 81 patients with the use of anesthesiologist-adjusted propofol infusion (study I) or target-controlled propofol infusion (study III). All sedations in study I were uneventful. In the study III desaturations were observed in 7(17 %), chin lift maneuver was used in 3(7 %) patients. Hypotension occurred in 1(2 %) patient. All SRAE occurred in patients treated with combination of propofol and alfentanil. Oversedation (MOAA/S=1) was observed in 50(62 %) patients. Arrhythmia and pulmonary aspiration were not observed.

TARGETED AND MEASURED PROPOFOL CONCENTRATIONS

When propofol administered with TCI the mean targeted propofol concentration was $2.2 (0.4) \text{ mcg} \cdot \text{ml}^{-1}$ needed for optimal sedation (III). In a random sample of patients (I) 52 blood samples were obtained (Table R6). The mean (SD) propofol plasma concentration did not differ significantly between the study groups and was $2.6(1.6) \text{ mcg} \cdot \text{ml}^{-1}$ (papilla cannulation, PC), $1.1(0.3) \text{ mcg} \cdot \text{ml}^{-1}$ (end of ERCP, EE) and $1.5(0.5) \text{ mcg} \cdot \text{ml}^{-1}$ (PC) $1.0(0.5) \text{ mcg} \cdot \text{ml}^{-1}$ (EE) in the propofol infusion and PCS groups respectively.

Table R6 C_p of propofol during ERCP

baseline	PI (n=10)										PCS (n=8)							
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
papilla cannulation	1.9	1.6	1.0	2.5	2.2	1.1	4.2	1.7	6.0	3.6	2.4	-	1.1	-	1.6	0.8	1.4	1.5
end of ERCP	0.9	1.0	0.7	1.6	0.8	1.0	1.0	1.4	1.0	1.2	0.7	0.4	0.5	1.8	0.9	1.5	1.2	0.8

RECOVERY

Sedation levels during recovery

In study I sedation levels were significantly deeper in the control group (propofol infusion) than in the PCS group after termination of ERCP and until twenty minutes post-procedurally. Also in study III sedation levels were significantly ($P = 0.047$) deeper in patients sedated by the anesthesiologist with the use of target-controlled infusion until 15 minutes post procedurally. In study IV patients sedated with combination of dexmedetomidine and PCS sedation levels were significantly deeper sedated until 20 minutes post-procedurally. In study II sedation levels did not differ markedly between study groups at the end of ERCP and during the recovery (Figures 6 A-D).

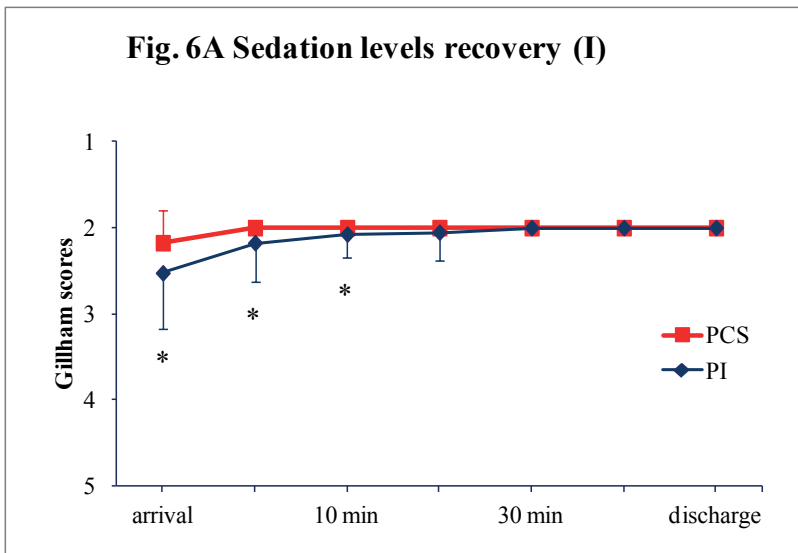


Figure 6A. Sedation levels during recovery (I). *Significant difference observed between PCS and PI during early 10 minutes in the recovery room, $P < 0.05$. PCS-patient-controlled sedation, PI-propofol infusion. Gillham sedation score: Awake and anxious-1, Awake not anxious-2, Speech slurred-3, Eyes closed, responds to speech-4, Eyes closed, responds to shaking-5, Unresponsive-6.

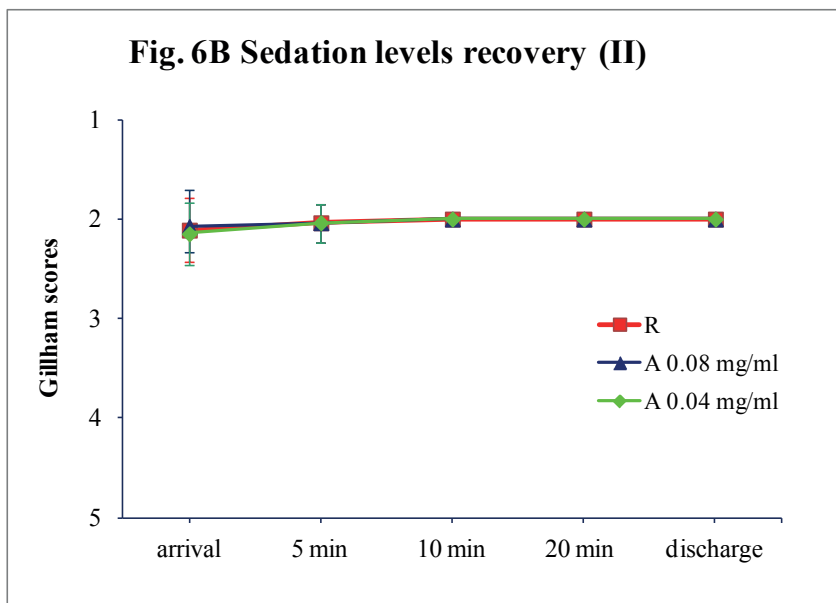


Figure 6B. Sedation levels during recovery (II). R-remifentanyl 0.01 mg · ml⁻¹; A 0.04 mg/ml-alfentanil 0.04 mg · ml⁻¹; A 0.08 mg/ml-alfentanil 0.08 mg · ml⁻¹. Gillham sedation score: Awake and anxious-1, Awake not anxious-2, Speech slurred-3, Eyes closed, responds to speech-4, Eyes closed, responds to shaking-5, Unresponsive-6.

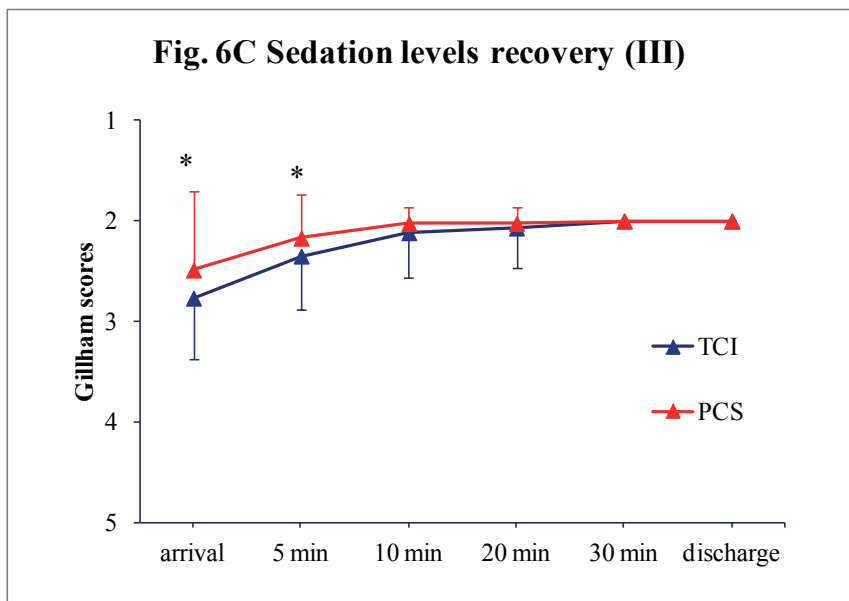


Figure 6C. Sedation levels during recovery(III). *Significant difference observed between PCS and TCI during early 5 minutes in the recovery room, P < 0.05. PCS-patient-controlled sedation, TCI-target-controlled infusion. Gillham sedation score: Awake and anxious-1, Awake not anxious-2, Speech slurred-3, Eyes closed, responds to speech-4, Eyes closed, responds to shaking-5, Unresponsive-6.

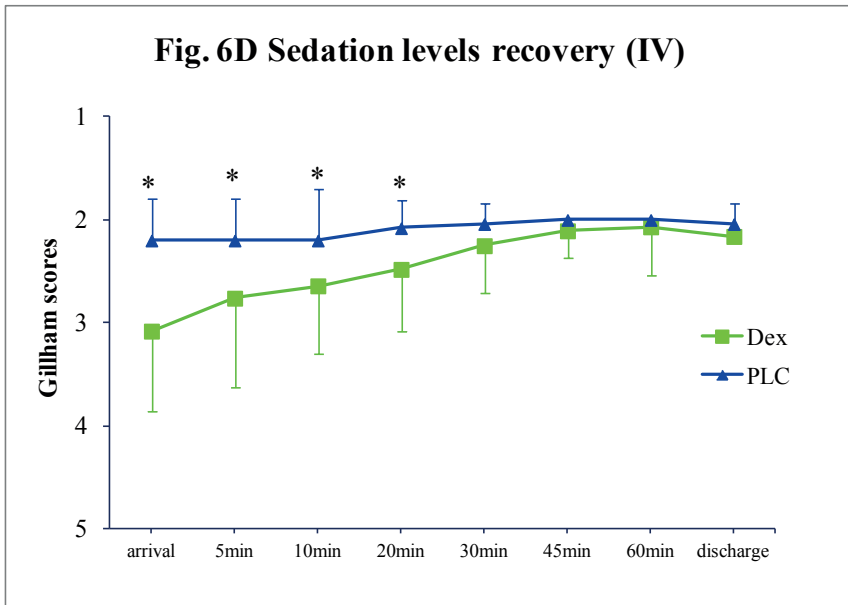


Figure 6D. Sedation levels during recovery(IV). *Significant difference observed between PLC and Dex during early 20 minutes in the recovery room, $P < 0.05$. PLC-placebo, Dex-dexmedetomidine. Gillham sedation score: Awake and anxious-1, Awake not anxious-2, Speech slurred-3, Eyes closed, responds to speech-4, Eyes closed, responds to shaking-5, Unresponsive-6.

Rapidity of recovery

The recovery of all patients in studies I-IV received propofol or propofol-opioid sedation was very fast. Near 90 % of patients were ready to discharge from the recovery room 10 minutes after ERCP termination. Aldrete scores did not differ markedly between study groups in studies I-III. In the study IV patients sedated with combination of dexmedetomidine and PCS had significantly ($P = 0.011$) lower Aldrete scores than sedated with PCS only until 5 minutes post-procedurally.

POST-PROCEDURAL PAIN AND NAUSEA

The intensity of post-procedural pain was low in all patients after ERCP and did not differ between the treatment groups in studies I-III (Figures 7 A-C).

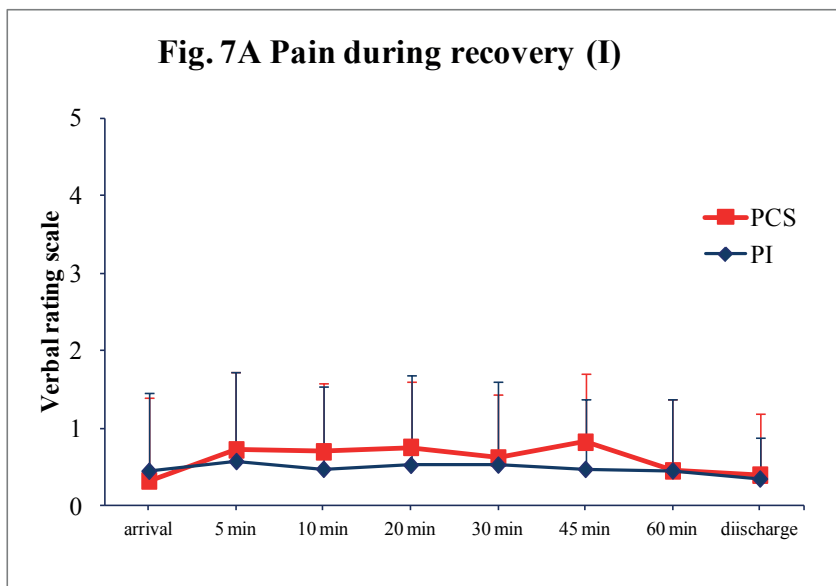


Figure 7A. Pain intensity during recovery (I). PCS-patient-controlled sedation, PI-propofol infusion. Intensity of post-procedural pain (verbal rating scale): 0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain.

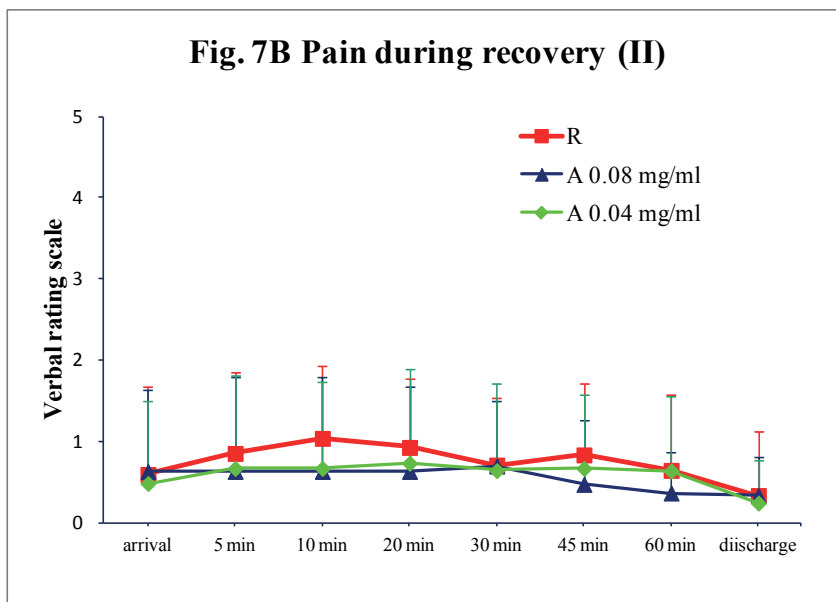


Figure 7B. Sedation levels during recovery (II). R-remifentanyl $0.01 \text{ mg} \cdot \text{ml}^{-1}$; A 0.04 mg/ml -alfentanil $0.04 \text{ mg} \cdot \text{ml}^{-1}$; A 0.08 mg/ml -alfentanil $0.08 \text{ mg} \cdot \text{ml}^{-1}$. Intensity of post-procedural pain (verbal rating scale): 0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain.

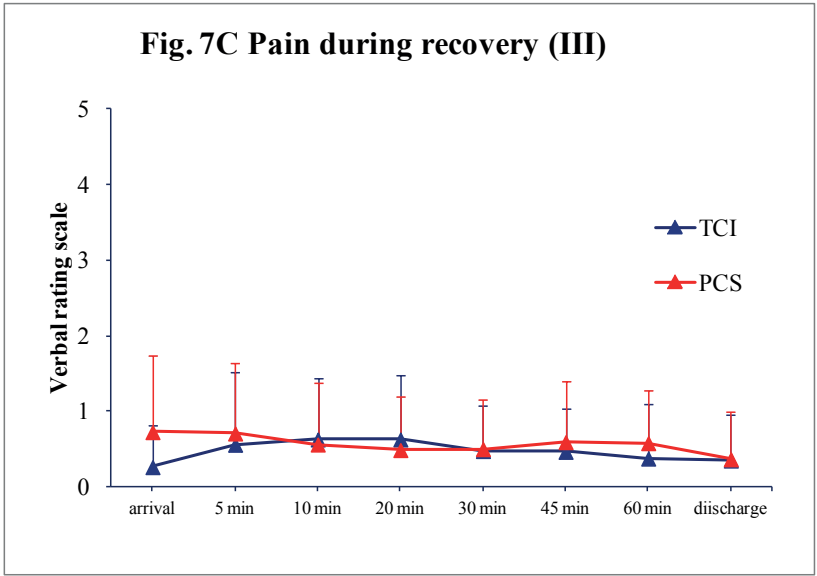


Figure 7C. Pain intensity during ERCP(III). PCS-patient-controlled sedation, TCI-target-controlled infusion. Intensity of post-procedural pain (verbal rating scale): 0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain.

Patients who received dexmedetomidine had significantly less pain than those who received placebo in the study IV (Figure 7 D).

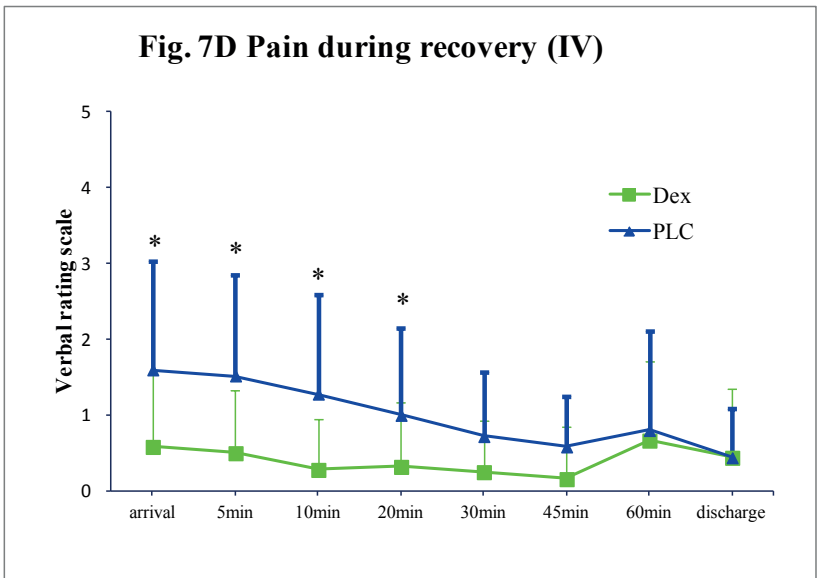


Figure 7D. Pain intensity during recovery(IV). *Significant difference observed between PLC and Dex during, $P < 0.05$. PLC-placebo, Dex-dexmedetomidine. Intensity of post-procedural pain (verbal rating scale): 0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain.

Nausea occurred in 21/212 (10 %) patients sedated with the use of PCS and in 7/81(8.6 %) patients from control groups (anesthesiologist administered propofol). In study II nausea happened significantly more often (P=0.044), in patients received remifentanil than in those sedated with the combination of alfentanil and propofol.

PATIENT SATISFACTION WITH SEDATION AND PREFERENCE FOR RECEIVED SEDATION

In all studies (I-IV) patient satisfaction was high (table R6) and did not differ significantly between study groups. Among patients who received PCS 198/212 (93 %) of patients would prefer PCS as a sedation method if ERCP will be repeated in future. Also in control groups preference for received sedation was 75/81(93 %).

Table R6 Patient's satisfaction with sedation and preference for received sedation									
Study	I		II			III		IV	
Study arm	PCS	PI	R	A1	A2	PCS	TCI	DEX	PLC
Patient satisfaction (mean (SD))	6.7 (0.5)	6.8 (0.5)	6.4 (1.2)	6.4 (0.7)	6.7 (0.5)	6.5(0.7)	6.6(0.7)	6.3 (0.7)	6.0 (1.3)
Preference in future Y/ N / don't know (n)	40 / 0 / 0	40 / 0 / 0	25 / 1 / 1	25 / 0 / 3	26 / 0 / 1	36 / 1 / 1	35 / 3 / 3	24 / 0 / 1	22 / 2 / 1

9 DISCUSSION

THE SUITABILITY OF PCS FOR ERCP

The results of studies I-IV showed that PCS is a very acceptable method of sedation for ERCP. The mean success rate of PCS, defined as lack of an anesthesiologist's adherence to the patient's sedation, in the studies I-IV was 92 %, which is substantially higher than that in two previous studies (Jowell PS et al. 1996, Gillham et al. 2001) describing PMS during ERCP. However, in these studies either midazolam or PMS with TCI was used. Using propofol alone or in the combination with remifentanil or alfentanil, the success rate of PCS during ERCP is comparable to that during colonoscopy (Crepeau T et al. 2005). The patient's and procedural factors predisposing failure of PCS are needed to reveal in the future. Our hypothesis that chronic alcohol abuse predispose to the failure of PCS could not be supported by the results of the study IV.

PROPOFOL CONSUMPTION

The results of studies (I, III) showed that in comparison to the AAS either with the use of manually adjusted or target-controlled propofol infusion, implementation of PCS leads to significant reduction of propofol consumption during ERCP. Although randomized comparisons between different methods of propofol administration during ERCP are lacking, this observation is in accordance with previous comparisons of AAS with PCS during endoscopy (Mandel J et al. 2008, Mandel J et al. 2010).

In the study of Heuss, comparing PCS with the nurse administered propofol sedation (NAPS) during colonoscopy propofol consumption was somewhat higher in patients received PCS (Heuss L 2004). At least few points needed to be considered in interpretation of this finding. Firstly, propofol boluses were used for sedation in the NAPS group. It was shown previously that in comparison to propofol infusion, bolus administration technique is associated with reduced consumption of propofol. On the other hand sedation with intermittent propofol boluses might be inappropriate during long-lasting ERCP (Newson C et al. 1995). Secondly, duration of colonoscopy was shorter in the NAPS groups and thirdly, significant difference between the study groups in propofol consumption was not achieved.

In study II propofol consumption did not differ between patients received remifentanil and alfentanil. The remifentanil and alfentanil doses used in the current study may have been equipotent. The true equianalgesic doses of remifentanil and alfentanil have not been defined previously in sedation with spontaneous respiration.

During propofol GA with the use of substantially higher doses of opioids than in PCS with spontaneous respiration, remifentanyl appeared equipotent to alfentanil in rates 1:4 to 1:20 (Philip BK et al. 1997, Jhaveri et al. 1997).

Anesthetic and analgesic sparing effects of dexmedetomidine are well documented (Bulow et al. 2007, Candiotti et al. 2010, Gerlach et al. 2009) in the previous studies. In the study IV patients received dexmedetomidine consumed significantly less propofol as well.

SEDATION RELATED ADVERSE EVENTS (SRAE)

In the present studies PCS appeared comparable with AAS in terms of adverse events and patient satisfaction with sedation. The results of studies I-IV showed incidence of 12 % in SRAE that is at the same frequency of those during AAS. Agostoni reported retrospectively the incidence of SRAE of 5.3 % in 2207 patients sedated with propofol during ERCP (Agostoni M et al. 2011). In the study of Berzin reporting prospectively 528 ERCP patients under propofol sedation or general anesthesia the incidence of SRAE was 21 % (Berzin T et al. 2008).

OPTIMAL COMPOSITION OF SEDATIVE MIXTURE AND REGIME OF ADMINISTRATION FOR PCS

The results of study II showed that combination of propofol and alfentanil for PCS during ERCP produces less respiratory depression and post-procedural nausea than combination of propofol and remifentanyl. This has not been reported previously. Randomized double-blind comparisons of different opioids for PCS are lacking. The benefits of opioid addition to propofol in sedative mixture for PCS are still unclear. In the majority of studies that describe PCS, either propofol alone or a combination of propofol and alfentanil have been used (Jowell P et al. 1996, Gillham M et al. 2001, Mandel et al. J 2008, Mandel J et al. 2010, Heuss L et al. 2004). According to these studies, adding an opioid increases the quality of sedation and decreases the need for interventions during the procedures (Mandel J et al. 2008). The similar dose of remifentanyl ($10 \text{ mcg}\cdot\text{ml}^{-1}$ in the sedative mixture) as has been found effective and safe in the previous studies of PCS for lithotripsy and colonoscopy (Mandel J et al. 2008, Alhashemi J et al. 2006).

SEDATION LEVELS

Deep sedation believed to be rather necessary for successful performance of ERCP (Chainaki I et al. 2011). The results of studies I-IV showed that if patient can choose

the necessary sedation level, deep sedation might be needed only in about 40 % of patients. In the studies I and III the decision of the depth of sedation was based on the previously established institutional practice or on the targeted C_E of propofol, and adjustments were made on the basis of physiological observations during the procedure. TCI may rationalize the dosing of intravenous anesthetics during general anesthesia, but the optimal concentrations of propofol for conscious sedation during ERCP remain to be defined.

The propofol plasma concentrations (PPC) have not been previously measured in patients sedated with PCS during ERCP. In the study of Irwin 36 patients treated with the use of patient-maintained propofol infusion, optimal sedation was provided at median target concentrations of $0.8 - 0.9 \text{ mg} \cdot \text{ml}^{-1}$ during surgical but not gastrointestinal procedures (Irwin et al. 1997). This and other studies (Schnider et al. 1998, 1999) showed a good correlation between predetermined plasma and effect site and actually measured blood propofol concentrations.

In a randomly chosen sample of patients (I) the actually measured plasma concentrations of propofol ($2.6 (1.6) \text{ mcg} \cdot \text{ml}^{-1}$) were surprisingly close to needed targeted effect-site concentration ($2.2(0.4) \text{ mcg} \cdot \text{ml}^{-1}$) (III). Yet there is a large variation between the plasma or effect-site concentrations of propofol and the optimal sedation both in the previous study (Irwin et al. 1997) and in ours. Although significant difference in PPC was not founded between patients received PI and PCS there was a tendency to a higher PPC during papilla cannulation in patients sedated with PI. Undoubtedly other than drug effects are accounted for the patients' tolerance of procedural discomfort during endoscopy.

DEXMEDETOMIDINE AS AN ADJUVANT FOR PCS

The results of study IV do not support the use of dexmedetomidine for sedation of patients with chronic alcohol abuse during ERCP. According to the best of current knowledge dexmedetomidine was not previously evaluated for procedural sedation of patients with chronic alcohol abuse in randomized controlled trials. The main disadvantage of dexmedetomidine in the study IV was significantly extended recovery from sedation. This observation is concordant with the study of Muller founded that patients sedated with dexmedetomidine during ERCP recovered significantly slower than received propofol and fentanyl for sedation (Muller S et al. 2008). Also dexmedetomidine might produce unfavorable hemodynamic effects such as hypotension and bradycardia (Jalowiecki P et al. 2005). Even though in the study IV severe bradycardia did not occurred in patients received dexmedetomidine, serious hypotension developed in one (4 %) patient. Because all patients in the study IV received glycopyrrolate this agent might be effective in the prevention of bradycardia produced by dexmedetomidine. Unstable hemodynamics may

be especially dangerous in patients suffered from cardiovascular diseases thus restricting dexmedetomidine use in these patients. Patients with cardiovascular diseases accounted for near 20 % of patients in the studies I-IV. Other disadvantages of dexmedetomidine for ERCP sedation showed in the study IV are long sedation induction time and insufficient sedative effect in the recommended administration regimen. Thus obvious conclusion should be made that administration of dexmedetomidine with the use of loading dose of $1 \text{ mcg} \cdot \text{kg}^{-1}$ over 10 minutes followed by continuous infusion of $0.7 \text{ mcg} \cdot \text{kg}^{-1}$ is inappropriate for sedation of patients with chronic alcohol abuse during ERCP. Clinical trials describing other regimens of dexmedetomidine administration during ERCP are lacking. Combination of dexmedetomidine infusion with self-administered propofol and alfentanil in the Study IV showed significant decrease in the success rate of PCS. The nature of this phenomenon remains unexplained. Dexmedetomidine believed produce cooperative sedation but influence of propofol and alfentanil on pharmacodynamics of dexmedetomidine is still unstudied. Combination of dexmedetomidine with PCS should be avoided. Significant reduction of propofol consumption in the study IV did not reduce the incidence of SRAE and thus clinical significance of this observation was fully invalidated by prolonged sedation induction time and recovery.

THE USE OF PCS AS AN INVESTIGATIVE TOOL

In study IV PCS was successfully used as a rescue sedation method for evaluation of dexmedetomidine efficacy during ERCP. To the best of current knowledge such application of PCS has not been described previously. So, the utilization of PCS might be extended for clinical trials describing efficacy of sedatives or/and sedative regimens, local anesthetics, regional anesthesia etc.

LIMITATIONS

This thesis has some limitations. All studies are single-centre trials. Due to relatively small number of patients conclusions regarding the safety of PCS are only preliminary. Emergencies and patients in ASA class IV as well as patients over 75 of age were not included in the studies. No psychological assessment was performed although psychological factors may influence on the individual needs of sedation. The design of studies I and III did not allowed double-blind administration of sedatives. In study III the discrimination of inadequate analgesia and sedation was based on clinical observations. Sedation scales used in studies I-IV are not validated for GI endoscopy. Anesthesiologist and anesthetic nurse were present all the procedure time. The recovery room personnel were not blinded to the study group allocation (studies I and III).

10 CLINICAL APPLICATIONS AND FUTURE STUDIES

On the basis of these findings PCS has been introduced as a primary method of sedation for patients undergoing ERCP in the Endoscopy unit in Meilahti hospital. Because PCS can be used without an anesthesiologist (Lee et al. 2004, Lee D et al. 2002, Kulling D et al. 2001, Heuss L et al. 2004,), this approach could be a cost-effective method. In a Finnish questionnaire survey the Finnish anaesthetic nurses expressed a very positive attitude on their independent role in the sedation outside the operating room (Vakkuri A et al. 2006). The wider use of PCS in the surveillance of an anesthetic nurse only, requires a composition of an appropriate educational programme, which is currently lacking. The advantages of PCS include undoubtedly that the patient can sedate him- or herself both mildly or deeply. In addition, PCS can be easily converted to a nurse controlled method when PCS fails.

However, there is an obvious need for future studies. Studies with sufficient amounts of patients must be carried to define the safety of PCS. In large-scale studies it would be possible to find out patients, to whom PCS should not be used. In addition, there is a lack of studies about the optimal composition of sedative mixtures and administration regimens for PCS. Use of lock-out time, background infusion and limitation of total dose of sedatives should be more carefully examined. Finally, the impact of the structure of infusion device, including the design of patient-administration button, should be taken into the consideration in the future plans.

11 CONCLUSIONS

The following conclusions can be made from the presented data:

- 1) Although sedation for ERCP could be successfully carried out by an anesthesiologist (AAS), patient-controlled sedation (PCS) is associated with decreased consumption of propofol, lighter levels of sedation and better recovery profile. Also deep sedation could be produced with PCS. Satisfaction rates are equal with both PCS and AAS. No difference exists in sedation related adverse events between PCS and AAS (I, III).
- 2) Remifentanyl causes more respiratory depression and nausea than alfentanil. The optimal concentration of alfentanil for PCS is $0.04 \text{ mg} \cdot \text{ml}^{-1}$ (II).
- 3) PCS is a suitable method of sedation of alcoholics during ERCP. Adding of dexmedetomidine to PCS reduces the consumption of propofol but impairs the quality of sedation, results in deeper level of sedation and delays recovery in comparison to PCS only (IV).
- 4) The success rate of PCS during ERCP is 88 - 100 % in selected patients (I-IV).

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