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OPIOID-FREE ANESTHESIA AND THE NURSE ANESTHETIST

Experiences in Sweden and the United States

Sofia Pihlblad
Daniel Verbeeck

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Abstract

Background: Opioid addiction and overdose deaths are growing problems in both Sweden and the United States. Opioids have played a major role in anesthesia since the 1960s, but cause numerous negative effects which are associated with patient suffering and increased cost of care. Evidence shows opioid-free anesthesia is emerging as a safe alternative, reducing the negative effects of opioids. Research on the nurse anesthetists' experiences of opioid-free anesthesia is limited. **Aim:** The aim of this study was to compare experiences among nurse anesthetists in Sweden and the United States with regards to their familiarity with opioid-free anesthesia, its perioperative risks and benefits, and the perceived connection between intraoperative opioids and postoperative addiction. **Methods:** A web-based survey was distributed to nurse anesthetists in Sweden and the United States. Data was analyzed using SPSS Statistics and presented descriptively, allowing comparisons between Sweden and the United States by displaying the data from the two nations in the same charts. **Results:** The nurse anesthetists from the United States had more experience with opioid-free anesthesia than the nurse anesthetists from Sweden. The majority of the nurse anesthetists from the United States agreed to all the benefits and disagreed to all the risks of opioid-free anesthesia listed in the survey. Many of the Swedish nurse anesthetists did not know the specific benefits and risks, nor which drugs should be included in an opioid-free anesthesia regime of care. Opioid addiction was perceived as a major problem in society by nurse anesthetists from both nations. **Conclusion:** American nurse anesthetists have more clinical experience and theoretical knowledge of opioid-free anesthesia compared to Swedish nurse anesthetists. More education is needed in Sweden to safely implement the concept. This study suggests that opioid-free anesthesia would be beneficial to Swedish nurse anesthetists' nursing priorities and postoperative patient outcome.

Keywords: Opioid-free anesthesia, OFA, General anesthesia, Non-opioid analgesics, Nurse anesthetist, Experience

Sammanfattning

Bakgrund: Opioidberoende och överdosrelaterade dödsfall är ett växande problem i både Sverige och USA. Opioider har haft en viktig roll inom anestesin sedan 1960-talet, men orsakar flera negativa effekter som kan leda till lidande för patienten och ökade vårdkostnader för samhället. I evidensbaserad forskning framträder opioidfri anestesi som ett patientsäkert alternativ som minskar de negativa effekterna av opioider. Forskningen på anestesisjuksköterskans upplevelse av opioidfri anestesi är begränsad. **Syfte:** Syftet med denna studie var att jämföra upplevelser och erfarenheter mellan anestesisjuksköterskor i Sverige och USA av förtrogenheten med opioidfri anestesi, dess perioperativa risker och fördelar, samt uppfattningen av ett samband mellan intraoperativa opioider och postoperativt beroende. **Metod:** En webbaserad enkät skickades ut till anestesisjuksköterskor i Sverige och USA. Data analyserades i SPSS Statistics och presenterades deskriptivt. Jämförelserna mellan Sverige och USA möjliggjordes genom att visa data från de två länderna tillsammans i samma diagram. **Resultat:** Anestesisjuksköterskorna i USA hade större erfarenhet av opioidfri anestesi än anestesisjuksköterskorna i Sverige. Majoriteten av anestesisjuksköterskorna i USA instämde med alla fördelar och instämde inte med alla risker med opioidfri anestesi som angavs i enkäten. Många av de svenska anestesisjuksköterskorna kände inte till de specifika fördelar och risker som angavs i enkäten, eller vilka läkemedel som borde inkluderas i en vårdplan för opioidfri anestesi. Anestesisjuksköterskor från båda länder ansåg att opioidberoende är ett stort problem i samhället. **Slutsats:** Anestesisjuksköterskor i USA har mer klinisk erfarenhet och teoretisk kunskap om opioidfri anestesi jämfört med svenska anestesisjuksköterskor. I Sverige behövs mer utbildning för att konceptet ska kunna implementeras säkert. Denna studie tyder på att opioidfri anestesi skulle vara fördelaktig för både svenska anestesisjuksköterskors omvårdnadsprioriteringar och för patienten i det postoperativa förloppet.

Nyckelord: Opioidfri anestesi, OFA, Generell anestesi, Icke-opioida analgetika, Anestesisjuksköterka, Upplevelse, Erfarenhet

Preface

The authors would like to thank Dr. John McDonough at the University of North Florida for his contribution to the design of our survey, and Dr. Pether Jildenstål at the University of Gothenburg for his guidance during the writing of this thesis. Myrah Chavez and Jonathan Vicencio, SRNAs at the University of North Florida, have been helpful in correcting grammar and wording. We also send a warm *thank you* to all the nurse anesthetists and students who took the time to answer our surveys, in both Sweden and the United States, without whom this study would not have been possible.

Abbreviations and definitions

ASA – **American Society of Anesthesiologists physical status classification system:**

ASA I healthy patient
ASA II mild systemic disease
ASA III severe systemic disease
ASA IV severe systemic disease with constant threat to life
ASA V moribund patient not expected to survive without operation
ASA VI organ donor (ASA House of Delegates/Executive Committee, 2014)

BIS – Bispectral index

Cardiac output – "The volume of blood passing through the heart per unit of time. It is usually expressed as liters (volume) per minute" (Karolinska Institutet, 2016a)

CNS – Central nervous system

CRNA – Certified Registered Nurse Anesthetist in the United States

EEG – Electroencephalography

GABA – Gamma-aminobutyric acid

Hemodynamic – "The movement and the forces involved in the movement of the blood through the cardiovascular system" (Karolinska Institutet, 2016d)

Induction – transition from being awake to under general anesthesia (Karolinska Institutet, 2016c)

MAC – Minimum alveolar concentration, (of anesthetic gases)

Multimodal – "The treatment of a disease or condition by several different means simultaneously or sequentially" (Karolinska Institutet, 2016b)

NMDA – N-methyl-D-aspartate

Nociception – "Sensing of noxious mechanical, thermal or chemical stimuli by nociceptors. It is the sensory component of visceral and tissue pain" (Karolinska Institutet, 2016e)

NSAID – Nonsteroidal anti-inflammatory drugs

Nurse anesthetist – Used in this thesis to mean American CRNA and/or Swedish nurse anesthetist

Opioid-free anesthesia – Anesthesia without intraoperative opioids and an aim to reduce perioperative opioids, commonly abbreviated OFA (Kremer & Griffis, 2018)

Opioid-sparing anesthesia – Anesthesia with reduced opioid doses due to multimodal analgesia (Kremer & Griffis, 2018)

PONV – Postoperative nausea and vomiting

PRST – Blood pressure, heart rate, sweating and tears

RCT – Randomized controlled trial

Rf AnIva – Riksföreningen för anestesi och intensivvård, National Association for Anaesthesia and Intensive Care

SRNA – Student Registered Nurse Anesthetist in the United States

SSF – Svensk sjuksköterskeförening, The Swedish Society of Nursing

TIVA – Total intravenous anesthesia

Viscera – "Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen" (Karolinska Institutet, 2016f)

δ – delta

κ – kappa

μ – mu

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Introduction

Opioid addiction and overdose deaths are increasing problems in both Sweden and the United States (National Institute on Drug Abuse, 2019; Public Health Agency of Sweden, 2019). Opioids have a central role in suppressing pain stimuli, and are therefore commonly used in general anesthesia. However, opioids have several negative side effects such as: nausea, constipation, respiratory depression, stimulation of cancer cell proliferation and addiction (Kremer & Griffis, 2018). Several studies have suggested that a person who has never used opioids before surgery may have an increased risk to develop an addiction to opioids after surgery with traditional opioid-based anesthesia (Koepke et al., 2018). In recent years, methods to deliver general anesthesia without the use of opioids, so-called Opioid-Free Anesthesia (OFA), have been developed. Through randomized controlled trials (RCT), opioid-free anesthesia has been shown to minimize the negative side effects of opioids, while still delivering a safe and stable anesthesia. Nurse anesthetists are the main providers of anesthesia in both Sweden and the United States, and as such they have a responsibility for perioperative patient care and the drugs administered during anesthesia, as well as to stay continuously educated and updated on current evidence-based practice in their field (Riksföreningen för anestesi och intensivvård & Svensk sjuksköterskeförening [Rf AnIva & SSF], 2012). In the United States, opioid overdose deaths and opioid addiction is being discussed as the “opioid epidemic”, a public health emergency. According to nurse anesthetists Kremer and Griffis (2018), this calls for a paradigm shift in the treatment of pain, consequently focusing on the exclusion of opioids from anesthesia. The investigators and authors of this study participated in an Exchange Student Program with the University of North Florida, which sparked an interest to compare Swedish and American nurse anesthetists’ experiences with opioid-free anesthesia.

Background

General anesthesia

Current medical practice requires anesthesia to perform humane surgical procedures on patients. To achieve optimal surgical conditions, the patient needs to be motionless, be unaware about what is happening and feel no pain. Historically, the first time this was achieved was in 1846 with the administration of diethyl ether (ether) during a surgical procedure. At the time, pain free surgeries were regarded as a miracle and this new phenomenon was named Anesthesia, from Greek meaning without sensation. Countless breakthroughs have since been achieved in the evolution of anesthesia in the one hundred seventy years since it was first implemented. The three primary groups of drugs used in modern general anesthesia are hypnotics, analgesics and neuromuscular blocking agents. To anesthetize a patient for general anesthesia, a combination of several different drugs needs to

be administered either through inhalation or intravenous access (Boon, Martini, & Dahan, 2018; Robinson & Toledo, 2012).

Hypnotics

Hypnotic drugs are used to cause sleep and ensure that the patient is not aware during surgical procedures. Nitrous oxide gas was used in the early 1800s during dental procedures, but to provide tolerable pain levels the patient risked hypoxia (Robinson & Toledo, 2012). This led to the introduction of ether and the dawn of a revolution in pain free surgeries. Ether is a liquid drug, and could be administered through intermittent drips on a fabric placed over the mouth of the patient who inhaled it as a vapor. It has a stimulating effect on cardiac output and respiratory rate and causes bronchodilation. Ether, unlike other hypnotics, also has an analgesic effect both intra- and postoperatively (Chang, Goldstein, Agarwal, & Swan, 2015). However, ether is a volatile liquid with high flammability, a prolonged induction time, high incidence of nausea and vomiting and a persistent unpleasant odor. In 1932, the barbiturate sodium thiopental was developed for use as an induction agent. However, it was found to have a strong depressing effect on cardiac output. Propofol was introduced in 1977, and had the advantage of having a shorter recovery time than sodium thiopental, as well as having antiemetic properties (Robinson & Toledo, 2012). Halothane (the forerunner of today's Isoflurane, Desflurane and Sevoflurane), discovered in the 1950s, completely replaced ether in the 1960s. The modern inhalation gases have the advantage of being less flammable and more potent, while causing less nausea and vomiting than ether, but also have a depressing effect on cardiac output and the respiratory drive. Consequently, in addition to analgesic drugs, heart monitoring and oxygen supplementation are needed when using modern hypnotics (Chang et al., 2015).

Neuromuscular blocking agents

To create optimal conditions for the surgeon to perform the procedure, the patient needs to be immobile. Temporary immobility can be achieved by a muscle relaxant. Muscle relaxation improves working conditions: for example during intubation, by relaxing the jaw for easy manipulation and better visualization of the vocal cords. Before the introduction of curare in 1942, immobility was achieved by increasing the anesthetic doses, which not all patients tolerated hemodynamically. The increased use of muscle relaxation led to the need to secure the airway quickly, which spurred the invention of the laryngoscope and endotracheal intubation (Robinson & Toledo, 2012). Modern medicine currently uses two different groups of neuromuscular blocking agents, depolarizing and non-depolarizing, pharmacologically different, but with similar effects. Administering a neuromuscular blocking agent does not create hemodynamic changes in the patient, nor does it have an analgesic effect (Boon et al., 2018).

Analgesics

Historically, distraction was used as an analgesic strategy during surgery. Analgesic drugs have a pain relieving effect, and include inhaled anesthetic agents, local anesthetics, opioids and some non-opioid drugs (Kremer & Griffis, 2018; Robinson & Toledo, 2012). For a

description of the non-opioid drugs included in the survey questions, please see Appendix 4: Non-opioid drugs.

General anesthesia and pain

The International Association for the Study of Pain (2017) define pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (p1). Pain is a complex experience, greatly influenced by emotional, cultural and cognitive components (Bridgestock & Rae, 2013). The fact that pain is defined as an emotional experience implies that a person must be conscious and cognitive while experiencing pain. Thus, it can be considered inaccurate to refer to a patient as having "pain" during general anesthesia (Forget, 2019). However, with modern hypnotic drugs, nociception, which is the physiological detection of and reaction to harmful stimuli, persists despite hypnosis, unless blocked using intraoperative analgesic drugs. Upon surgical tissue damage, nociceptors in the skin and viscera send "pain"-signals to the central nervous system (CNS), via fast myelinated Aδ nerve fibers and slower unmyelinated C nerve fibers. This leads to stimulation of the sympathetic nervous system and is usually observed intraoperatively as increased blood pressure and heart rate, sweating and tears. (Cividjian et al., 2017).

Opioids

Opioids are a group of potent analgesic drugs known as narcotic analgesics. Opioids work mainly by binding to opioid receptors, primarily the mu (μ), kappa (κ) and delta (δ) receptors in the CNS, where they have an agonistic effect as they inhibit the afferent pain signals before they reach the brain (Kremer & Griffis, 2018).

The use of opioids for treating pain dates back to the early 1800s, when Friedrich Sertürner, a German pharmacist, discovered how to isolate Morphine from opium (Trang et al., 2015). But it was during the 1960s, when the Belgian Paul Janssen developed the synthetic opioid fentanyl, that opioids became widely used in general anesthesia (Mulier & Dekock, 2017). During the latter part of the 20th century, fentanyl has been followed by numerous synthetic fentanyl analogues intended for use in anesthesia, for example sufentanil, alfentanil and remifentanil. These new synthetic drugs are designed with increased potency, more rapid onset and shorter duration to be more adapted to the anesthesia process (FASS, 2018b).

Opioids in anesthesia

Since patients under general anesthesia do not experience pain, opioids are administered for their sympathetic suppressive effect of the reaction to surgical stimuli, rather than their analgesic effect. Opioids counteract the elevation of blood pressure and heart rate associated with nociception (Lavand'homme & Estebe, 2018).

Before the 1960s, high doses of inhalation gases and barbiturates were the common methods of induction, causing a strong depressing effect on cardiac output. By combining inhalation gas and barbiturates with opioids, a synergistic effect was created, which led to a dose reduction in the hypnotic drugs required for induction.

Opioids were responsible for both suppressing the sympathetic system and offering hemodynamic stability, especially for patients who suffered from undiagnosed cardiovascular diseases, which was more prevalent before the 1960s (Koepke et al., 2018). Opioids even have a crucial role in the protective mechanism of myocardial ischemic preconditioning. By activating δ and κ receptors, opioids reduce myocardial tissue damage during ischemia (Kremer & Griffis, 2018; Tanaka, Kersten, & Riess, 2014).

Currently, one of the most common anesthesia regimes of care in Sweden is total intravenous anesthesia (TIVA), with propofol and remifentanil administered via target controlled infusion (TCI)-pumps, and titrating the anesthesia according to the cerebral and plasma concentration level (Spetz, 2018). The fentanyl analogue remifentanil, ideal for use during general anesthesia with its almost immediate onset and ultra-short duration, can be titrated to adequate effect with ease. Remifentanil does not accumulate during continuous infusions, hence offering rapid recovery (Kremer & Griffis, 2018; Santonocito, Noto, Crimi, & Sanfilippo, 2018).

Negative effects of opioids

Opioids have numerous negative side effects. Respiratory depression following a high dose of opioids is caused by a disruption in the respiratory center in the brainstem. It can last for several hours, suppressing the respiratory drive normally activated by increased levels of carbon dioxide (Kremer & Griffis, 2018).

The occurrence of postoperative nausea and vomiting (PONV) is more common when the patient has been administered opioids (Kremer & Griffis, 2018). PONV is associated with patient suffering and increased cost of care due to extended hospital stays (Hooper, 2015). Assessing the patient's individual risk factors of developing PONV, the Apfel Score uses a 0-4 point scale. It was validated for patients undergoing anesthesia with benzodiazepine for premedication, induction with thiopental and fentanyl, and the use of volatile anesthetic gas as maintenance (Apfel, Läärä, Koivuranta, Greim, & Roewer, 1999).

Urinary retention is caused by opioids tightening the sphincter muscle, and constipation can occur when opioids affect the intestines and decrease gastric motility. Both have the potential for causing serious complications and extended hospital stays. Orthostatic hypotension and syncope are caused by venous pooling when rising from a horizontal position. This is more common when the patient has been administered opioids, and can interfere with early ambulation (Hontoir et al., 2016; Kremer & Griffis, 2018).

Opioid-induced hyperalgesia is a paradoxical increased sensitivity to painful stimuli following opioid administration, leading to higher postoperative analgesic requirement. This is likely caused by central sensitization to pain (Santonocito et al., 2018). This opioid paradox is described as "the more opioids used intraoperatively, the more opioids required postoperatively" (Koepke et al., 2018, p. 2).

Opioid tolerance is when the same dose of opioids gradually generates less analgesia, thus requiring higher doses over time. It is caused by repeated opioid administration, which reduces the activation of opioid receptors achieved by a given dose (Santonocito et al., 2018).

Opioid dependence is caused by opioid stimulation to release the neurotransmitter dopamine, which is linked to feelings of well-being and reward, as well as increased risk-taking to seek pleasure. Gradually, because of tolerance, less dopamine is released with every opioid dose, leading to pursuit of higher doses, and the emergence of negative emotions upon withdrawal from opioids. Opioid withdrawal, stopping, or decreasing opioid use also gives rise to several negative symptoms such as tachycardia, hypertension, diarrhea, insomnia and increased pain (American Psychiatric Association, 2013). This may eventually lead to addiction, which is the most severe form of substance-use disorder with substantial loss of self-control (Volkow, Koob, & McLellan, 2016).

Opioid prescription and abuse

In 2017, the opioid epidemic in the United States was declared a public health emergency by the government. Opioid abuse and addiction is not a new occurrence, but the recent outbreak can be traced back to the late 1990s, when a different perspective on pain as well as its treatment was adopted. Guidelines developed in the United States promoted the assessment and treatment of acute and chronic pain. Pain control policy during that time encouraged treatment with opioids. Opioids were promoted as safe and with a low risk of causing addiction. The fact that the pharmaceutical industry both funded the policy and had policy developers on payroll led to an increase in opioid prescriptions (Koepke et al., 2018). Since the year 2000 there has been a quadruple increase in deaths due to overdoses involving prescriptions and illegal opioids (Mauermann, Ruppen, & Bandschapp, 2017).

Postoperative prescription of opioids is associated with a higher risk to develop long term use, abuse, addiction and overdose. The longer the first period of opioid use, the higher the risk to develop a long-term addiction. Studies exploring the quantity of pills prescribed after different surgeries found that it could range from 0 to 120 pills. A prescription of an opioid after surgery is often the beginning of a chronic opioid use, and pills not taken postoperatively could be used for nonmedical purposes by someone other than the patient (Brandal et al., 2017; Koepke et al., 2018; Kremer & Griffis, 2018).

Opioid dependence has become wide spread in the United States, where opioid overdose currently is the leading cause of accidental deaths, exceeding deaths due to motor vehicle

accidents. The opioid epidemic and the negative effects of opioids following anesthesia has spurred the clinical trials to reduce the use of opioids in anesthesia practice (Koepke et al., 2018).

Opioid overdose deaths

In Sweden, 626 narcotics related deaths occurred in 2017, of which more than 95% were related to opioids. Non-voluntary intoxication (overdose) was reported as the most common cause of narcotic related death, as well as the cause that has increased the most in recent years (Public Health Agency of Sweden, 2019). With a population of 9.995 million in 2017, this equals to 6.0 of 100,000 inhabitants. The corresponding number in the United States was 47,600 opioid related overdose deaths. With a population of 325.7 million in 2017, this equals to 14.6 of 100,000 inhabitants (National Institute on Drug Abuse, 2019). According to these numbers, opioid overdose death is more than 2.4 times as common in the United States than in Sweden.

Multimodal analgesia

Suppressing the hemodynamic reaction to surgical tissue damage can be achieved with different groups of opioid and non-opioid analgesic drugs. Using two or more different drugs, creating a synergistic or additive effect to reduce the doses of individual drugs, is called multimodal analgesia. Achieving the additive effects can minimize negative side effects while still managing to achieve adequate analgesia. Combining a reduced dose of a hypnotic agent with one or several analgesic agents during induction of anesthesia can suppress the hemodynamic reaction of intubation (Mauermann et al., 2017; Robinson & Toledo, 2012). Regional anesthesia with neuraxial and peripheral nerve blocks can be combined with general anesthesia to reduce opioid use (Koepke et al., 2018). N-methyl-D-aspartate (NMDA) receptor antagonists, alpha 2-agonists, magnesium sulfate, intravenous lidocaine and corticosteroids all have analgesic or antinociceptive effects and can be used as adjuvants or substitutes for opioids during anesthesia (Kremer & Griffis, 2018; Mauermann et al., 2017) The same principle can be applied to postoperative analgesia. The most common non-prescription, non-opioid analgesic drugs used to treat postoperative pain are paracetamol and COX-inhibitors, or nonsteroidal anti-inflammatory drugs (NSAID). Administered together, paracetamol and NSAIDs reduce the need of opioids postoperatively, thus having an opioid-sparing effect. Multimodal analgesia is the foundation of opioid-free or opioid-sparing techniques (Kremer & Griffis, 2018; Mauermann et al., 2017).

Opioid-free anesthesia

Opioid-free anesthesia, as the name implies, is anesthesia without the use of opioids. Generally, opioids are avoided both pre- and postoperatively when the concept is clinically practiced, thus only relying on opioids as a last resort rescue analgesic (Koepke et al., 2018).

Clinical trials with opioid-free anesthesia

Many researchers have conducted clinical trials to validate the implementation of an opioid-reduced or opioid-free approach to the perioperative process.

An RCT by Bakan et al. (2015) investigated opioid-free anesthesia comparing the drugs propofol, dexmedetomidine and lidocaine versus remifentanil during laparoscopic cholecystectomies. A significant reduction of the need of rescue analgesics was observed early postoperatively, later equal results were found. The difference in occurrence of PONV was not statistically significant, but the use of rescue antiemetic drugs decreased. The conclusion was that opioid-free anesthesia can be an alternative, especially for patients at high risk for PONV.

An RCT by Hontoir et al. (2016) hypothesized that opioid-free anesthesia with ketamine, lidocaine and clonidine would give higher rates of self-defined patient comfort in recovery after breast cancer surgery, compared to remifentanil-based anesthesia. The result showed a statistically significant increase of comfort with the opioid-free group, however the increase was slightly smaller than what the researchers deemed clinically relevant. Opioid-free anesthesia was still determined as a safe method for the patient group.

Brandal et al. (2017) implemented an opioid-free routine for colorectal surgery using ketamine, lidocaine and neural blocks, and evaluated the impact it had on opioid consumption. Although the intraoperative use of opioids was significantly reduced, no significant difference in discharge dose and quantity of prescription opioids was seen. Patients with low pain scores at discharge, low consumption of opioids postoperatively, and no opioid use preoperatively still received opioid prescriptions. This suggests that the behavior of the physician, rather than the patient's medical condition, may be the primary determinant for prescriptions of opioids.

The evidence shows that opioid-free anesthesia yields equal or improved postoperative patient outcome regarding negative effects such as PONV and postoperative pain. Opioid-free anesthesia is emerging as a valid alternative to traditional opioid-based anesthesia and may assist in solving the opioid epidemic (Koepke et al., 2018).

Although these clinical trials validated one combination of non-opioid drugs for a specific surgical procedure, more studies are needed to cover all fields of surgery, and the best available evidence needs to be determined using meta-analysis. Current evidence has not yet determined the ideal combination of non-opioid analgesics, nor validated the regime for a large number of surgical procedures (Mulier & Dekock, 2017).

Depth of anesthesia

Guedel's classification of anesthesia was developed by the American anesthesiologist Arthur Guedel in 1937 and was originally based on ether anesthesia. The classification defines four stages of the depth of anesthesia, with the third stage being divided into four planes of surgical anesthesia. The clinical signs used by Guedel are respiration, eye activity, pupil dilation and reflex, eyelid reflex, and muscular responses such as swallowing. These are still used today, although newer anesthetic agents, opioids and muscle relaxants alter the clinical responses, rendering Guedel's classification slightly obsolete (Jameson & Sloan, 2006). Opioids, for example, are known to constrict the pupil in a way that was not observed by Guedel. Furthermore, the classical stages in Guedel's classification can be concealed when using multiple drugs to achieve multimodal analgesia or balanced anesthesia (Rani & Harsoor, 2012).

A similar assessment tool is known as the PRST-score and was developed in the 1980s. This uses the clinical signs blood pressure, heart rate, sweating and tears (PRST) to evaluate the adequacy of anesthesia. It has later been proposed that the PRST-score is a better indication of the adequacy of analgesia, that is suppression of responses to painful stimuli, rather than the hypnosis or depth of anesthesia (Warrén Stomberg, Sjöstrom, & Haljamae, 2001).

To avoid both too deep anesthesia, with a risk of impaired postoperative cognitive function, and too shallow anesthesia, with a risk of awareness, different techniques to measure the depth of anesthesia have been developed (Sinha & Koshy, 2007). Since the effect of various drugs and doses is individual, merely measuring drug concentration in µg/ml (TCI) or minimum alveolar concentration (MAC) is not always perceived to be sufficient. The brain is the target organ for all general anesthetics, and therefore different variants of electroencephalography (EEG) can be used. Bispectral index (BIS) is one such method, where the EEG is processed and converted to display a number between 0 and 100. A value between 40 and 60 is consistent with adequate anesthesia. A lower index value is correlated with longer periods of burst-suppression and isoelectric EEG, meaning heavily suppressed cortical activity. However, any modified EEG-method is less accurate in monitoring the depth of anesthesia when drugs that do not target the gamma-aminobutyric acid receptor ($GABA_A$) are used, such as ketamine and nitrous oxide (Rani & Harsoor, 2012). This means that BIS and other EEG-based depth of anesthesia monitors may be less reliable when used together with opioid-free anesthesia.

Role of the nurse anesthetist

The Swedish healthcare system aims to provide care on equal terms for the entire population. Healthcare shall be practiced with respect for the equal value of all people and the dignity of all individuals. Priority is given to those with the greatest needs, and the healthcare system strives to prevent illness (SFS 2017:30).

In both Sweden and the United States, anesthesia is administered by nurse anesthetists. A nurse anesthetist can independently induce, maintain, and awaken a patient from general anesthesia, with only varying degrees of support from a physician anesthesiologist. The nurse anesthetists' main priority is anesthesiological care of the patient throughout the perioperative setting, based on the resources and needs of every individual. This requires knowledge of both medicine and nursing science (Rf AnIva & SSF, 2012).

The Swedish Society of Nursing collaborates with the American initiative Quality and Safety Education for Nurses to promote the six core competences of the specialist nurse, one of which is evidence-based practice (Disch, 2012). Evidence-based practice is to apply the best available scientific evidence from research to implement good, effective care of the individual patient. In the nursing process, all steps need to be scientifically substantiated by evidence-based practice. In scientific medical research, RCTs and meta-analysis of RCTs are regarded as the gold standard for evidence (Johansson & Wallin, 2013; Walker & Avant, 2019).

In the United States, nurse anesthetists are Advanced Practice Nurses, meaning they practice with a high degree of autonomy. In some states, they are able to assess, plan and administer anesthesia without supervision of a physician.

In Sweden, the nurse anesthetist is required indirect supervision by a physician, who assesses the patient and prescribes the anesthesia. Patients classified as American Society of Anesthesiologists (ASA) physical status I and II can be anesthetized by the nurse anesthetist independently for elective procedures, while collaboration with a physician anesthesiologist is required for ASA III to V-patients and emergency procedures (Rf AnIva & SSF, 2012).

The length of the postgraduate education required to become a nurse anesthetist is also different, being one year in Sweden and three years in the United States. Additional recertification is required every two to four years in the United States (National Board of Certification and Recertification for Nurse Anesthetists, 2019). American nurse anesthetists are trained to establish regional anesthesia through for example spinal and epidural blocks, which are performed by physician anesthesiologists in Sweden.

Both nurse anesthetists and physician anesthesiologists have a responsibility for the drugs they administer during anesthesia (HSLF-FS 2017:37). In Sweden, the nurse anesthetists work on prescriptions from the physician, while in the United States, the nurse anesthetists have a greater responsibility to individually plan and choose their anesthesia. The role of the nurse anesthetist regarding choice and administration of opioids may therefore be different in Sweden and the United States. However, it is their understanding and approach to opioid-free alternatives that could be vital for patients in both nations.

The majority of articles on opioid-free anesthesia found in scientific databases are medical studies with quantitative approaches. The nursing perspective of opioid-free anesthesia needs to be further researched, both quantitatively and qualitatively. As the nurse anesthetists are the ones closest to the patient during anesthesia, their experience and perspective of a possible paradigm shift in analgesia may prove important to investigate (Kremer & Griffis, 2018).

Problem statement

Opioids have played a central role in anesthesia for decades, despite their numerous negative side effects, which include respiratory depression, hyperalgesia, tolerance and addiction. Opioid addiction and opioid overdose deaths are increasing in both Sweden and the United States. Several RCTs show that opioid-free anesthesia can be an alternative to traditional opioid-based anesthesia, and nurse anesthetists need to be updated on the current evidence-based practice. However, there seem to be relatively few studies that illustrate the nurse anesthetists' perspective on administering opioid-free anesthesia. The role of the nurse anesthetist puts them in a position to influence both patient safety during anesthesia and postoperative patient outcome. Their role regarding choice and administration of opioids may be different in Sweden and the United States, but their understanding of and approach to opioid-free alternatives could be conclusive for patients in both nations. As the investigators participated in an Exchange Student Program with the University of North Florida, we had an interest in comparing Swedish and American nurse anesthetists' experiences with opioid-free anesthesia.

Aim

The aim of this study is to compare experiences among nurse anesthetists in Sweden and the United States with regards to their familiarity with opioid-free anesthesia, its perioperative risks and benefits, and the perceived connection between intraoperative opioids and postoperative addiction.

Methods

Design

In this study, a non-experimental quantitative method was utilized to perform a cross-sectional comparison between the experience of opioid-free anesthesia in the two pre-existing groups: Swedish and American nurse anesthetists. To reach as many nurse anesthetists in Sweden and the United States as possible, and increase the generalizability of the study, data collection was made with a web-based survey (Polit & Beck, 2012).

Development of survey

A web-based survey was developed in two language versions, one in English and one in Swedish (see appendices 1 and 2). Both versions consisted of the same 20 questions, and dichotomous questions were used to collect demographic data. The majority of the survey questions were multiple-choice questions on a Likert scale with five response alternatives: from *strongly agree* to *strongly disagree*. For specific statements regarding opioid-free anesthesia, a sixth response option was included: *I don't know*. Likert scales can be used to quantitatively compare attitudes between different people, as both the intensity and direction of opinions can be measured (Polit & Beck, 2012).

The surveys were designed using Google Forms with the intent to perform parallel comparisons. Dr. John McDonough, Director of the Nurse Anesthesia Program at the University of North Florida, collaborated with the principal investigators in the formulation of the survey questions, using his anecdotal clinical knowledge and with evidence from literature. Along with students from the University of North Florida and the University of Gothenburg, the questions were validated in the English language and Swedish translation respectively.

Sample

In Sweden, eight different anesthesia clinics were included in the survey: seven in southwestern Sweden and one in central Sweden. The inclusion criterion was to be an actively practicing nurse anesthetist in at least one of the chosen clinics. Contact was made by email to the operations managers of the clinics, and the nurse anesthetists were invited to participate after permission was granted by their respective managers. Consecutive sampling was used since all nurse anesthetists in the accessible population were invited to participate during the time period the survey was active. It was also a convenience sampling since the investigators chose to include easily accessible clinics (Polit & Beck, 2012).

In the United States, consecutive sampling was used as the survey was posted on-line in two closed groups for nurse anesthetists on the social media network Facebook. Inclusion criteria

were: to be a nurse anesthetist or student nurse anesthetist, have a Facebook membership and be a member of at least one of the closed groups. Both convenience and consecutive samplings are considered nonprobability (non-random) sampling methods (Polit & Beck, 2012).

Data collection

Initially, survey responses in the United States were collected in-person using a tablet with internet access at a hospital in North Florida. This was found to be ineffective considering the available time, and a link to the survey was instead posted on Facebook. The link was active for 26 days, although all responses came in the first week after publication.

In Sweden, the survey was distributed by email to nurse anesthetists by the operations managers of the participating clinics. The investigators did not have access to the emailing lists. In total, 318 Swedish nurse anesthetists received the invitation to participate in the survey, which was active for 14 days.

Data analysis

When the online surveys had been closed, the data was exported from Google Forms to Microsoft Office Excel (version 16.24). Answers on the Likert scales were converted to numbers, with 5 equaling *strongly agree*, 4 equaling *agree* and so on, with 0 being used to represent *I don't know*. The data was subsequently imported to SPSS Statistics (version 25.0, IBM Corp., Armonk, New York, USA), which was used to calculate descriptive statistics such as means, medians, standard deviations and valid percentages of answers. The answers on the Swedish and American versions of the surveys were handled separately. Data was then transferred back to Excel, which was used to create charts that compare the Swedish and American answers by showing the distribution of answers within each nation. In this step, Swedish and American data was displayed next to each other in the same charts. Throughout the process, both investigators were present to make sure no errors were made in the handling of the numbers.

Ethical considerations

The ethical principles for research involving human subjects stipulated by the Declaration of Helsinki were followed in the process of conducting this study (World Medical Association, 2013). There were no direct advantages or disadvantages for participants to partake in this non-experimental study. The information to the study participants (appendix 3) highlighted that participation was voluntary and explicitly stated any risks of joining the study.

Non-experimental studies can imply a certain risk of discomfort (Polit & Beck, 2012). A web-based survey is probably less prone to generate feelings of discomfort or bad memories than an interview situation, but opioids can be a sensitive topic for some people. It was therefore stressed that the option to leave certain questions unanswered existed. Advantages of participation could be that the study stimulated reflection upon opioid-free anesthesia, both within the individual nurse anesthetist and in the workplace. Participants could also contribute with valuable information for exchange of knowledge and experience between the two participating nations.

Consent to participate in the study was given when the survey was sent in electronically. Until that point, participation could be aborted and any answers would be erased. Questions about personal data such as age and gender were possible to leave unanswered if the participant so chose. Response data from the surveys was password protected and handled with confidentiality by none other than the principal investigators.

Results

The total number of respondents was 61 Swedish nurse anesthetists, and 107 American nurse anesthetists and student nurse anesthetists. One (1) respondent was regarded as internal omission and excluded from the Swedish survey since only one question had been answered (figure 1).

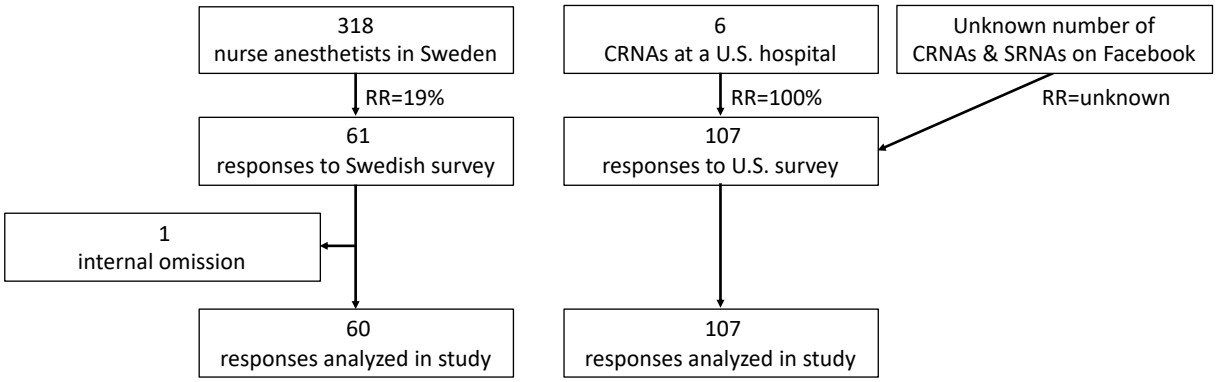

Figure 1. Flow chart of samples and responses in Sweden and the United States. (RR=response rate, CRNA=Certified Registered Nurse Anesthetist, SRNA=Student Registered Nurse Anesthetist)

Percentages are presented as valid percent (%) in all figures, meaning the percentage of valid answers to each question.

Demographics

No noteworthy difference was seen between the respondents reported age in Sweden and the United States. There was a gender distribution difference, with almost half of the American respondents identifying as male, while less than one fourth of the Swedish respondents identified as male. Years of experience was reported similarly, with the majority of the respondents in both nations having more than five years of experience. In the United States, some of the respondents were Student Registered Nurse Anesthetists. In Sweden, only nurse anesthetists responded to the survey. Respondents from Sweden most commonly practiced at a university hospital, while the American respondents were not asked to specify what type of hospital they practiced at.

	United States		Sweden	
Total number of responses	n107		n60	
Year of birth				
Responses	n104		n59	
Mean	1974,35		1973,54	
Median	1975		1975	
Std. Dev	10,53		11	
Minimum	1947		1954	
Maximum	1993		1989	
Gender				
Female	n57	53,3%	n46	76,7%
Male	n50	46,7%	n14	23,3%

	United States		Sweden	
Category				
Nurse anesthetist	n96	89,7%	n60	100%
SRNA	n11	10,3%	n0	0%
Years of experience in anesthesia				
0-2 years	n9	8,4%	n13	21,7%
3-5 years	n19	17,8%	n9	15%
6-10 years	n21	19,6%	n11	18,3%
11-15 years	n19	17,8%	n6	10%
≥ 16 years	n28	26,2%	n21	35%
Type of hospital				
University hospital			n25	41,7%
Region hospital			n19	31,7%
Hospital			n16	26,7%
Unspecified	n107	100%	n0	0%

Table 1. Demographic data presented as numbers, means, medians, standard deviation (Std. Dev) and valid percent (%). (SRNA=Student Registered Nurse Anesthetist)

Familiarity with opioid-free anesthesia

In the United States, 92% of the respondents reported familiarity with the concept of opioid-free anesthesia (agree + strongly agree; figure 2). The corresponding number in Sweden was 48%. Disagreement with the statement was 4% in the United States (disagree + strongly disagree). The corresponding number in Sweden was 44%.

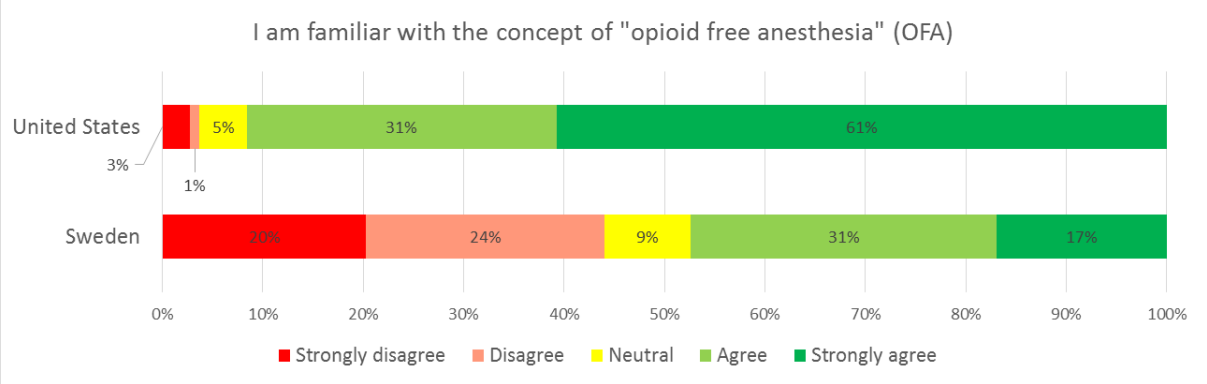

Figure 2. Familiarity with the concept of opioid-free anesthesia. (Sweden n=59, United States n=107)

This next question inquired both theoretical and practical knowledge about opioid-free anesthesia (figure 3). Approximately half of the respondents in the United States reported practicing opioid-free anesthesia clinically at least once a week. Clinical practice (at least: once a week + once a month + once a year) was reported by 69% of the American respondents, while this was reported by 24% of the Swedish respondents. More than 7 in 10 respondents in the United States reported having obtained knowledge about opioid-free

anesthesia from scientific articles. In Sweden, 55% reported having *no knowledge* about opioid-free anesthesia.

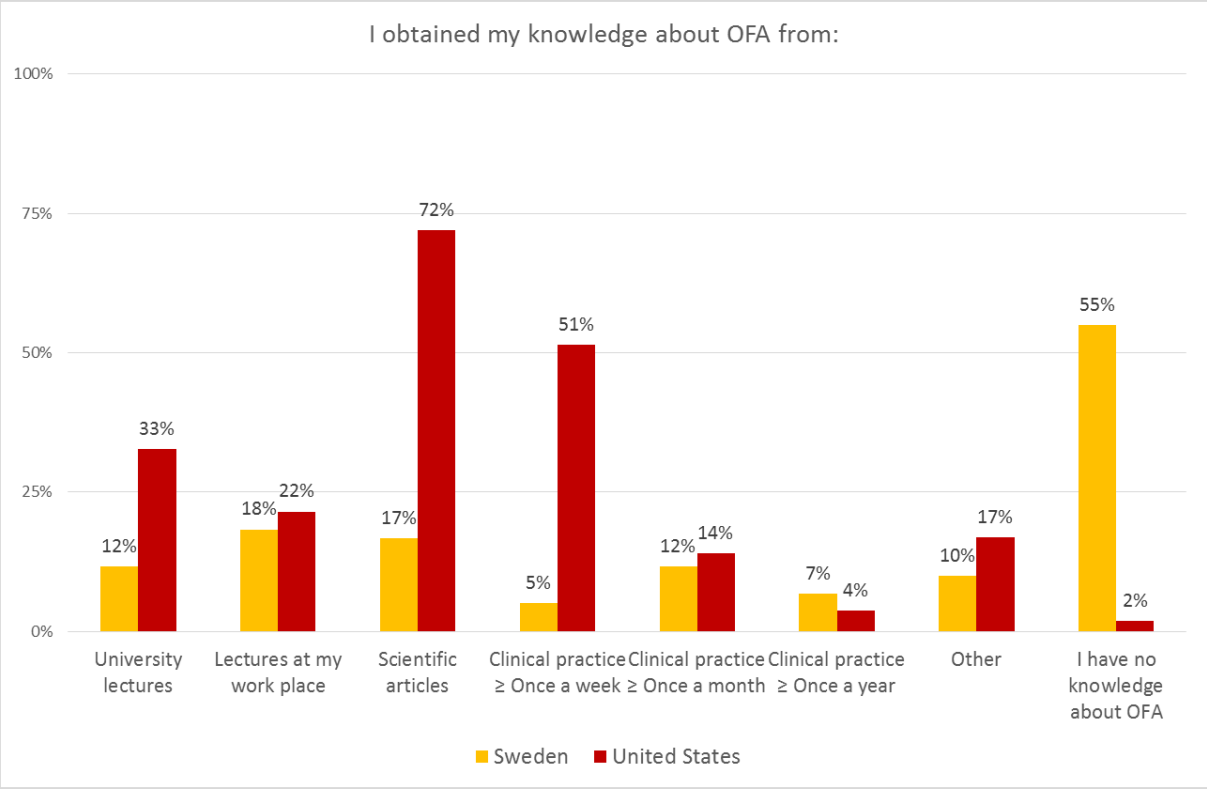

Figure 3. Origin of knowledge and frequency of clinical practice. (Sweden n=60, United States n=107)

Of the American nurse anesthetists, 85% reported agreement with the statement that the evidence supports the use of opioid-free anesthesia (agree + strongly agree; figure 4). In Sweden, the majority of the respondents chose the alternative *I don't know*. No one strongly disagreed to the statement in either nation, and only 2% of the American respondents disagreed.

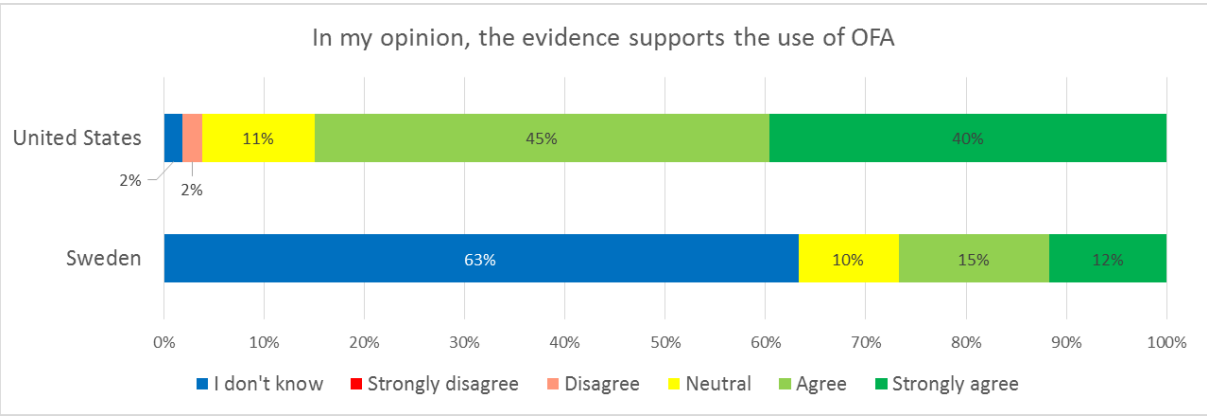

Figure 4. Opinion that the evidence supports the use opioid-free anesthesia. (Sweden n=60, United States n=106)

Benefits

The majority of respondents in the United States chose to agree and strongly agree with the statement that opioid-free anesthesia has benefits in all the categories in the question (appendix 5, figure 11). The categories with the most agreement were *avoiding constipation* (agree + strongly agree = 95%) and *risk of PONV* (agree + strongly agree = 92%). The least agreement was reported with the categories *postoperative pain* (agree + strongly agree = 72%) and *patients' desires* (agree + strongly agree = 72%).

The majority of the Swedish respondents chose the alternative *I don't know* on all the benefits except *risk of PONV* (appendix 5, figure 12). *Risk of PONV* was the only category where majority of the respondents agreed (agree + strongly agree) to opioid-free anesthesia having benefits.

Risks

The majority of the American respondents disagreed to the statement that opioid-free anesthesia has any of the listed intraoperative risks (figure 5). However, 20% of the respondents indicated that there was a risk of *heart rate: too high,* and 14% agreed that *blood pressure: too high* was a risk, although no one chose the alternative *strongly agree* to any risk. Fewer respondents thought that *heart rate: too low* and *blood pressure: too low* was a risk, with the percentages 2% and 3% respectively. In the Swedish survey, more than 60% of the respondents chose the alternative *I don't know* to all the categories.

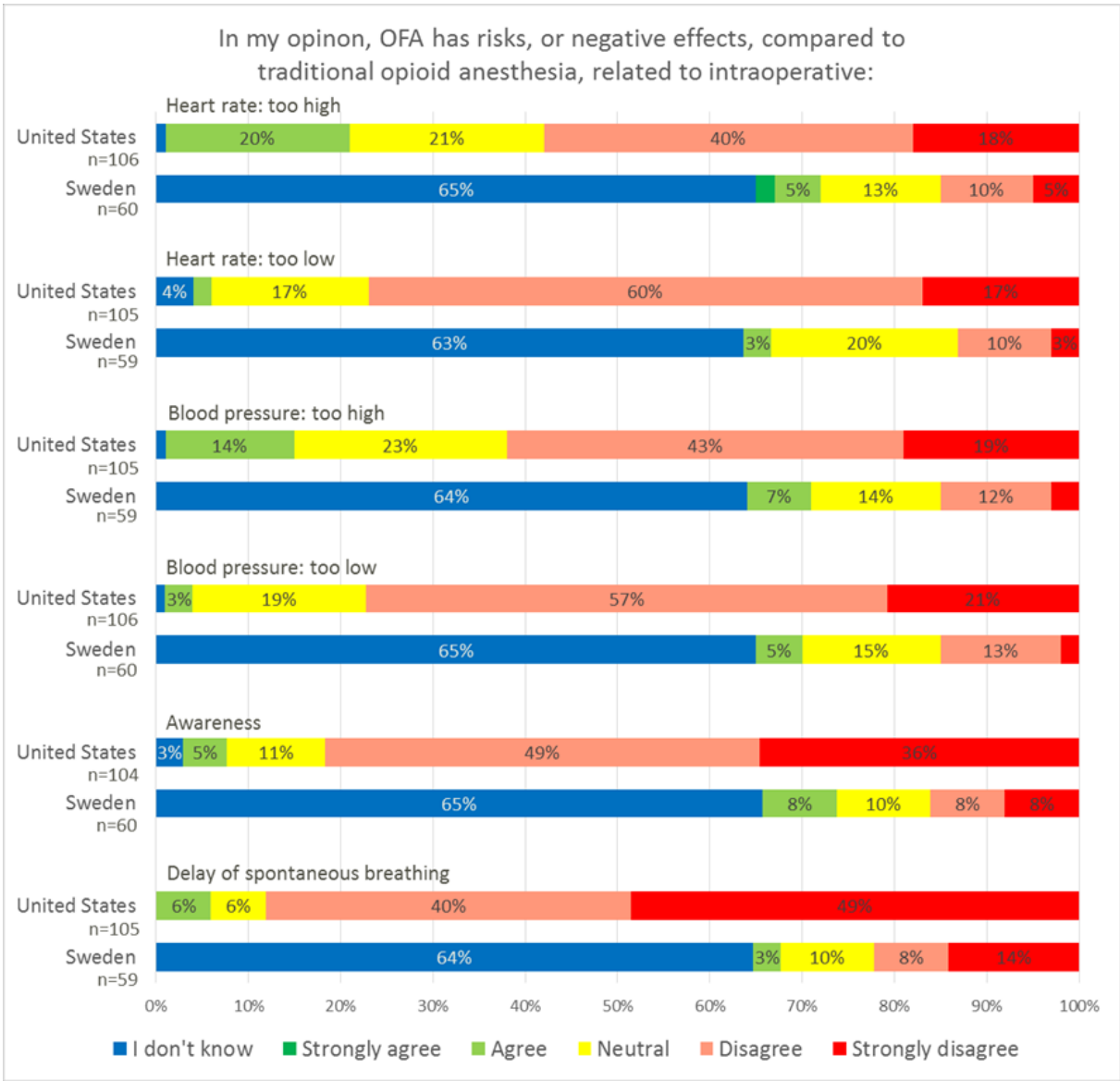

Figure 5. Comparison of perceived intraoperative risks of opioid-free anesthesia between Sweden and the United States. (n= see figure)

Drugs in the opioid-free anesthesia regime of care

Of the drugs listed, only nitrous oxide received less than 50% of the American respondents' agreements to be included in an opioid-free anesthesia regime of care (appendix 5, figure 13). The most popular drugs to be included were ketamine, lidocaine, propofol, ketorolac and paracetamol, with more than 90% agreements respectively (agree + strongly agree).

The most popular drugs to include according to the Swedish respondents were paracetamol, propofol, lidocaine and clonidine. *I don't know*-answers ranged from 36% to 75%, with the least amount of *I don't know*-answers on paracetamol and the most on magnesium (appendix 5, figure 14).

Respondents were also asked to report their familiarity with the non-opioid drugs listed in the survey. The majority of the American respondents chose to strongly agree with being familiar with all the non-opioid drugs listed in the survey except clonidine (appendix 5, figure 15).

The Swedish respondents reported the least familiarity with magnesium and dexmedetomidine, with less than 50% agreements respectively (appendix 5, figure 16).

Measuring the depth of anesthesia

Differences were reported in the perceived importance of depth of anesthesia monitoring between Sweden and the United States (figure 6). In Sweden, 72% of respondents thought it was important to measure depth of anesthesia, while only 31% thought it was important in the United States.

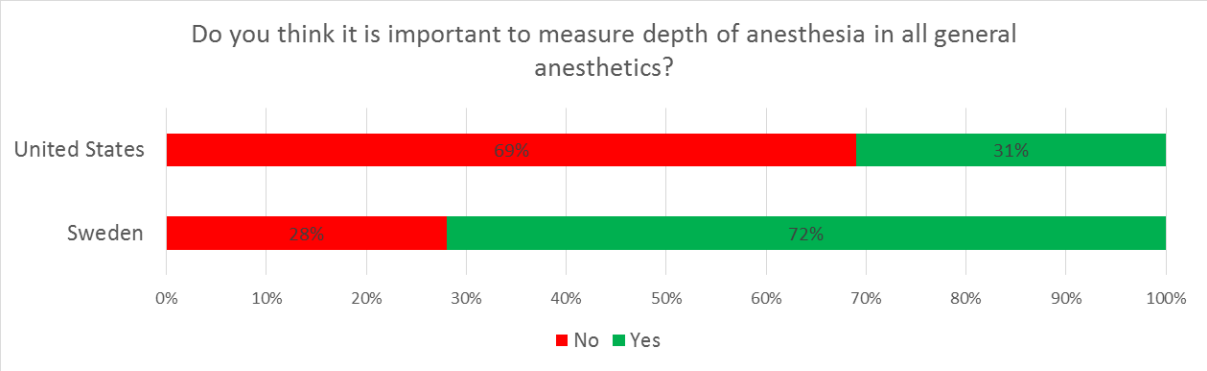

Figure 6. Measuring depth of anesthesia in all general anesthetics. (Sweden n=60, United States n=107)

Respondents who answered *yes* were asked to specify under which circumstances depth of anesthesia was monitored (appendix 5, figure 17). In the United States, the two most frequently selected alternatives were *only for patients "at risk"* and *rarely or never*, and in Sweden, the most frequently selected alternatives were *when a monitor is available* and *always.*

The perceived importance of measuring depth of anesthesia in opioid-free anesthetics differed from the perceived importance of measuring in all general anesthetics (figure 7). In the United States, a higher percentage of respondents thought it was important to measure depth of anesthesia in opioid-free anesthesia than in all general anesthetics. The alternative *I don't know* was selected by 38% in Sweden, and 11% in the United States. Of all questions in this survey, this question generated the highest percentage of *I don't know*-answers from respondents in the United States.

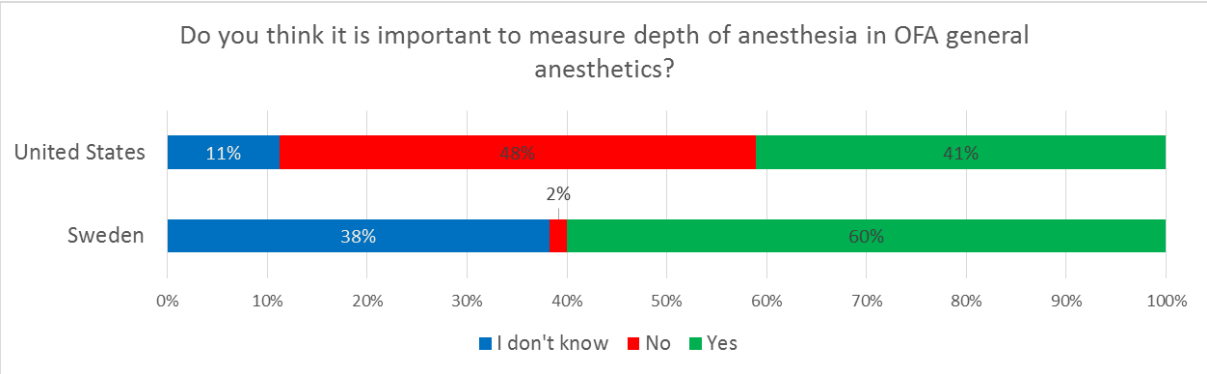

Figure 7. Measuring depth of anesthesia in opioid-free anesthesia general anesthetics. (Sweden n=60, United States n=107)

Opioid-free anesthesia and opioid addiction

In the United States, 93% of the respondents considered opioid addiction to be a major problem in society (agree + strongly agree), while in Sweden, 69% agreed and strongly agreed (figure 8). In Sweden, 32% were neutral, disagreed or strongly disagreed to the statement, while in the United States, the corresponding percentage was 8% of the respondents.

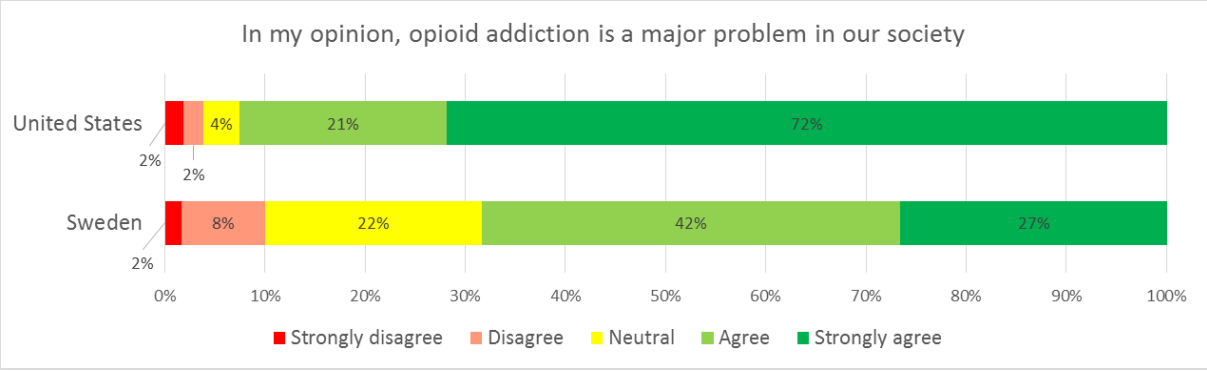

Figure 8. Opinions of opioid addiction being a major problem in society. (Sweden n=60, United States n=107)

In both nations, the majority of the respondents had the opinion that patients who have a history of opioid abuse should receive opioid-free anesthesia (figure 9). In the United States, 85% agreed to the statement (agree + strongly agree), while the corresponding number in Sweden was 51%. One third of the Swedish respondents chose the alternative *I don't know*.

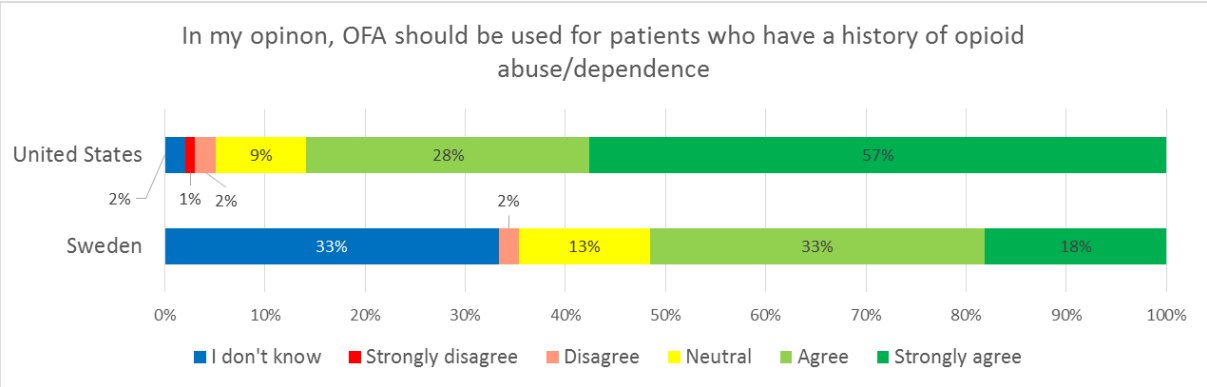

Figure 9. Opioid-free anesthesia for patients with opioid abuse or dependence. (Sweden n=60, United States n=106)

The majority of the American respondents agreed to the statement that administering opioids intraoperatively can lead to opioid dependence (agree + strongly agree; figure 10). The corresponding number in Sweden was 22%. Disagreement to the statement was reported by 27% of American and 45% of Swedish respondents (disagree + strongly disagree).

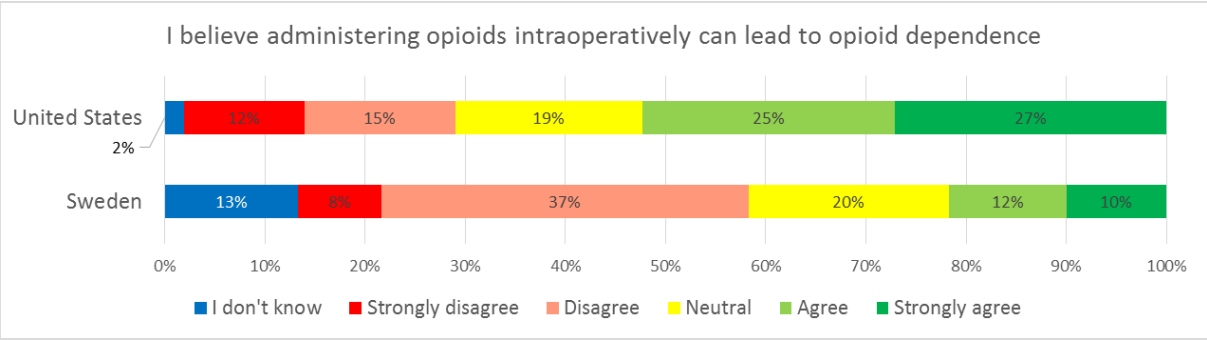

Figure 10. Intraoperative opioids leading to opioid dependence. (Sweden n=60, United States n=107)

Side effects to avoid

As a last question, the respondents were asked which side effects of anesthesia were perceived as important to avoid in all anesthesia practice. This was a question designed to identify the nurse anesthetists' priorities in the perioperative patient care. The majority of the American respondents agreed to all the statements (appendix 5, figure 18). The only category with total agreement was *PONV* (agree + strongly agree = 100%).

The majority of the Swedish respondents also agreed to all the statements (appendix 5, figure 19). The categories with the most agreements were *PONV* and *postoperative pain* (agree + strongly agree = 100%).

Discussion

Method discussion

Design

The aim of this study was to compare experiences of opioid-free anesthesia between nurse anesthetists in Sweden and the United States. Since the aim was to compare these pre-existing groups, a non-experimental quantitative method was appropriate (Polit & Beck, 2012). This may have led to some disadvantages compared to a qualitative method, the most prominent being that a qualitative study could have given a deeper understanding of the nature and expression of these experiences. To be able to compare experiences between Swedish and American nurse anesthetists, first the experiences needed to be made quantifiable. By describing complex phenomena such as experiences by using numbers, the investigators have used a positivist approach. Positivism implies that an objective reality exists, which is studiable and measurable, and that this reality exists independently of human observation (Polit & Beck, 2012). To measure this reality, we have collected empirical data, compared it and drawn conclusions from it.

Sample

The target population was all actively practicing nurse anesthetists in Sweden and the United States. The accessible population depended on the method of distribution of the survey, and efficiency in the distribution was valued highly due to time constraints. No advantage was seen from using probability (random) sampling instead, since the aim was to include as many nurse anesthetists as possible. Probability sampling would rather lead to random exclusion of some nurse anesthetists, as to decrease the sample size (Polit & Beck, 2012), which we did not consider necessary.

In Sweden, the sample consisted of nurse anesthetists in southwestern and central Sweden. Distribution to the entire nation's nurse anesthetists was desired but not possible, leading to a possible convenience sampling bias (Polit & Beck, 2012). In the United States, the survey was distributed via Facebook. This led to an unintended inclusion criterion of being a registered user of the social media platform.

The response rate in Sweden was 19 %. In the United States, the response rate is unknown, because membership sizes of the closed groups used to distribute the survey is unclear. Possible numbers range up to approximately 25.500. The investigators consider this number to be unsuitable for response rate calculation, since group membership does not necessarily equal becoming aware of the survey. Social media content distribution is based on complex algorithms, which do not guarantee visibility of the survey to all members unless actively searched for, neither do they distribute content randomly (Peruta & Shields, 2018). The fact that American responses were only collected within the first week of publication indicates

that the survey may not have reached the intended population or sample, rendering response rate calculation very difficult.

As we used a web-based survey, a low response rate could be expected. This may have led to nonresponse bias, since nonresponse is also not considered to be random (Polit & Beck, 2012). This can be considered a weakness in our study, as an interest in the study topic is known to increase the individual's willingness to participate. More nurse anesthetists with particularly strong opinions, both positive and negative on opioid-free anesthesia, may have chosen to participate than the average nurse anesthetists in the two respective nations. This may be particularly prominent in the American version of the survey, since it was distributed using social media and not through the practitioners' workplaces, as employee surveys tend to have higher response rates (Saleh & Bista, 2017). This may decrease the generalizability of our study. However, the investigators consider the distribution between answers to be wide enough to indicate that nonresponse bias still is low, and therefore believe some generalization can be made.

In Sweden, to increase the validity and generalizability of the study, the investigators sought to include many different specialties of anesthesia clinics. However, some of the operations managers in Sweden expressed reluctance to let their nurse anesthetists participate, owing to a belief that they would not be able to answer the questions, since the clinic did not practice opioid-free anesthesia. After clarifying to the operations managers that the survey was designed for all nurse anesthetists to be able to answer all the questions, these clinics also agreed to be included in the study. Yet some nurse anesthetists may have had the same opinion, thus choosing not to participate, leading to another source of possible nonresponse bias (Polit & Beck, 2012).

Data collection

Data collection was made with a web-based survey. This has several advantages compared to interviews or surveys on paper. It is for example time- and cost effective since it can reach a large amount of people in a short amount of time. It is also a means to guarantee anonymity and may therefore give more truthful answers. Provided that the survey is well developed, any bias from the investigators can be eliminated. Disadvantages could be that questions can be misunderstood, closed questions with given answers can give less information than open questions, and the response rate tends to be low (Polit & Beck, 2012).

The investigators first used a tablet with the survey, collecting answers in-person at a hospital in the United States. This method yielded a high response rate, although it was inefficient related to the available time, whereby subsequent publication on Facebook was chosen. While the investigators are aware that this lack of rigor in the sampling plan may decrease the reliability of the study, the six responses collected in-person were ultimately not perceived to affect the final results enough to warrant their exclusion (Polit & Beck, 2012).

Validity and reliability

Great importance is placed on the survey's validity, ensuring that the survey questions measure according to our aim. The survey becomes an instrument for data collection and its construction and structure are imperative for the quality of the collected data. (Polit & Beck, 2012). Since no pre-existing survey existed that could be used to answer our aim, a new survey had to be developed. The surveys in the present study were developed with the assistance of Dr. John McDonough, Director of the Nurse Anesthesia Program at the University of North Florida, and our supervisor at the University of Gothenburg, who both also validated the questions. There is congruence between the wording of questions between the two survey versions, as students from both universities helped to validate the survey and its translation, and their feedback was used to improve the final version (Trost & Hultåker, 2016). However, during the data analysis, it became apparent that the wording of some questions could be slightly unspecific, leading to possible misinterpretations. For example, in the questions about the drug lidocaine, it was its intravenous use we wanted to inquire about, but this was not specified, and the question could therefore be interpreted as regarding its use as a local anesthetic. This can affect the validity of the question, and must be considered when analyzing the responses.

In the survey, terms such as *tachycardia* and *hypotension* were deliberately not used, as these commonly have fixed numerical definitions, not necessarily reached during general anesthesia. *Too high* or *too low* were used to more easily let the respondents define and determine the risks of blood pressure and heart rate levels, as these usually differ between patients.

For specific statements regarding opioid-free anesthesia, a sixth response option was included: *I don't know*, as not to force respondents to express an opinion on statements they may not have knowledge about. Omissions, *I don't know* and *neutral* responses were analyzed separately, since they represent different attitudes in the study population (Stocké, 2006). The *I don't know*-response option was used extensively in the Swedish version of the survey, and its inclusion is believed to have increased the validity of the results (Trost & Hultåker, 2016).

Generalizability

The survey was distributed to two Swedish anesthesia clinics that have been conducting pilot studies on opioid-free anesthesia. This may have caused selection bias in the Swedish results, decreasing the generalizability towards the target population of Swedish nurse anesthetists (Polit & Beck, 2012). Of the recruited sample in Sweden (318 nurse anesthetists), 51 nurse anesthetists were practicing at these two clinics, thus constituting 16% of the sample. Due to the anonymity of the survey, it is not possible to discern the response rate of these two clinics with opioid-free anesthesia pilot studies. They may therefore constitute a larger proportion of the analyzed responses. To increase the generalizability of the results, larger sample sizes and further research is required in both nations (Polit & Beck, 2012).

Result discussion

When comparing the results between the United States and Sweden, the American respondents had more experience with opioid-free anesthesia. The majority of the American respondents agreed to all the benefits and disagreed to all the risks of opioid-free anesthesia listed in the survey questions. In the questions regarding benefits, risks and which drugs should be included in an opioid-free anesthesia regime of care, many of the Swedish respondents chose the alternative *I don't know*. Respondents from both nations stated that opioid addiction was a major problem in society.

Familiarity with opioid-free anesthesia

Swedish and American nurse anesthetists reported considerably different familiarity with the concept of opioid-free anesthesia. Almost all the American respondents reported being familiar with the concept (figure 2), and more than half of the respondents clinically practiced opioid-free anesthesia at least once a week (figure 3). The situation was reported quite differently in Sweden, with only less than half of the respondents being familiar with the concept, and almost no one practicing opioid-free anesthesia every week. Hypothetically, the opioid epidemic in the United States may be a contributing factor to this difference, as it may lead to a higher general awareness of the negative and potentially lethal side effects of opioids (Koepke et al., 2018). The opioid epidemic is also commonly referenced in scientific articles on opioid-free anesthesia (Forget & Cata, 2017; Koepke et al., 2018; Kremer & Griffis, 2018; Mauermann et al., 2017).

72% of the American respondents, and only 17% of the Swedish respondents, reported having read scientific articles about opioid-free anesthesia. In contrast to 24% of the Swedish nurse anesthetists reporting having clinically practiced opioid-free anesthesia, 17% is a worryingly low number. Considering the requirements of evidence-based practice and continuous education, stipulated in the description of competence for the nurse anesthetist, the reading of scientific articles should be an integral part of the nursing profession (Rf AnIva & SSF, 2012). This is also reflected in the survey question about whether the evidence supports the use of opioid-free anesthesia, where the majority of the Swedish respondents chose the alternative *I don't know* (figure 4). This may be evidence of a cultural or educational difference in the nurse anesthetist profession, regarding the acquisition of evidence-based knowledge, between the two nations. While the American nurse anesthetists may see it as their personal responsibility to seek and read current scientific articles, the Swedish nurse anesthetists may rely more on oral information from colleagues and the traditions and experiences of the clinic. As recertification is required in the United States, but not in Sweden, American nurse anesthetists may be more inclined to continuously pursue evidence-based knowledge.

Several of the articles referenced in this study were written by American researchers, and several RCTs have been conducted in American clinics (Brandal et al., 2017; Koepke et al., 2018; Kremer & Griffis, 2018; Ziemann-Gimmel, Goldfarb, Koppman, & Marema, 2014).

However, the majority of the referenced articles have been from Europe, and it may only be a matter of time before the concept of opioid-free anesthesia is widely adopted in Sweden. There have been pilot studies in Sweden assessing the possibility of developing opioid-free anesthesia regimes of care. At one clinic in central Sweden, opioid-free anesthesia is being practiced as routine.

Benefits

Figure 11 in appendix 5 shows that the majority of the respondents in the United States agreed that opioid-free anesthesia has benefits for all the categories in the statement, compared to traditional opioid-based anesthesia. For example, benefits regarding the risk of PONV was one of the categories with the most agreements. PONV is a well-known problem related to anesthesia and has been prevalent since the introduction of ether. It is more common when opioids are included in anesthesia (Kremer & Griffis, 2018). Our findings are consistent with the evidence presented in the RCTs by Bakan et al. (2015) and Ziemann-Gimmel et al. (2014), who all found that opioid-free anesthesia lowered the incidence of PONV and the use of antiemetic rescue drugs. Today, the most widely used method of identifying patients at risk for developing PONV is the Apfel score. The four variables included in the Apfel score are gender, smoking, history of motion sickness or PONV and the use of postoperative opioids (Apfel et al., 1999). Moreover, the Apfel score was validated through the use of opioids as part of the anesthesia. If opioids are excluded from anesthesia, would the Apfel score still be valid as a predictor for PONV? This is unclear, as new evidence-based practice may be needed to validate alternate PONV-risk assessment tools for use with opioid-free anesthesia. However, an ongoing RCT comparing opioid-free versus opioid-based anesthesia, specifically looking at postoperative opioid related side effects, is still using the Apfel score to assess and prevent PONV (Beloeil et al., 2018).

One of the categories of benefits was *patients' desires*. This category generated one of the smallest amounts of agreements from the United States, though still a majority (appendix 5, figure 11). We can only speculate as to the reasoning behind the respondents' answers, but one explanation may be that the nurse anesthetists regard some patients' preoperative wishes to not receive opioids as a valuable reason to administer opioid-free anesthesia. With the spread of the opioid epidemic, and society becoming more aware of the negative effects of opioids, a growing proportion of patients may actively request opioid-free anesthesia in the future.

The last question in the survey summarized what the nurse anesthetists perceived as important to avoid in all anesthesia practice, thereby identifying their priorities in the perioperative patient care, which correspond to the Code of Ethics of the International Council of Nurses (Rf AnIva & SSF, 2012). When comparing the Swedish responses to this question with the American responses to the question about the benefits of opioid-free anesthesia, similar patterns can be seen. First, the majority of all respondents agreed to all the categories. The categories regarding *PONV*, *urinary retention* and *constipation* were the categories with the

highest congruence between answers. For example, the American respondents regarded reduced PONV as one of the clearest benefits of opioid-free anesthesia compared to opioid-based anesthesia, while the Swedish respondents all agreed that PONV was important to avoid. A conclusion could be that the experience of the American nurse anesthetists suggests opioid-free anesthesia would be beneficial to the priorities of the Swedish nurse anesthetists.

Risks

The majority of the respondents from the United States disagreed to the statements that opioid-free anesthesia has any of the intraoperative risks listed in the survey (figure 5). However, some of the respondents also agreed to the risks. The risks of the patient having *heart rate* and *blood pressure: too high* were perceived as the two greatest risks (20%, 14%), while *heart rate* and *blood pressure: too low* were the least perceived risks (2%, 3%), compared to traditional opioid-based anesthesia. In the RCT by (Bakan et al., 2015), the opioid-free anesthesia group had significantly higher blood pressure and heart rate during anesthesia than the control group. The opioid-free anesthesia was delivered using dexmedetomidine, lidocaine and propofol. This is consistent with our findings about the American nurse anesthetists' perception of risks during opioid-free anesthesia, although it must still be considered that the majority of the respondents did not perceive *too high* blood pressure and heart rate as risks. Consequently, blood pressure and heart rate may be higher during opioid-free anesthesia, while not necessarily becoming *too high*.

The risks regarding blood pressure and heart rate can also be related to another question in the survey, namely the one inquiring about which drugs to be included in an opioid-free anesthesia regime of care. Among the responses from American nurse anesthetists (appendix 5, figure 13), ketamine was one of the most popular drugs to include in opioid-free anesthesia (95%). Ketamine is known to induce both tachycardia and hypertension. Conversely, clonidine was one of the least popular drugs to include (61%), and bradycardia and hypotension are some of its side effects (Bekhit, Navab, Ghobrial, & Aust, 2015). This may partially explain our findings. Another explanation could be that some respondents relate the omission of opioids from anesthesia to an increased nociceptive ("pain") response in the patient during surgery, compared to traditional opioid-based anesthesia. Increased nociceptive response would imply inadequate analgesia and in turn cause higher blood pressure and heart rate (Cividjian et al., 2017; Forget, 2019). Other drugs that affect the hemodynamics are magnesium, which lowers heart rate but not blood pressure, dexmedetomidine, which lowers both heart rate and blood pressure, and propofol, which lowers blood pressure through vasodilation (Bekhit et al., 2015; Forget & Cata, 2017; Hirsch, Fox, & Kaye, 2015).

The risk with the most disagreement was *delay of spontaneous breathing*. This can probably be explained by the avoidance of the otherwise common side effect of opioid-induced respiratory depression (Kremer & Griffis, 2018).

Drugs in the opioid-free anesthesia regime of care

An interesting comparison can be made between figures 13 and 16 in appendix 5. Figure 13 shows which drugs the American respondents think should be included in opioid-free anesthesia, and figure 16 shows the Swedish respondents' familiarity with the same drugs. Three of the drugs identified by the American respondents as popular to include in an opioid-free anesthesia regime of care were not very familiar to the Swedish respondents. These were magnesium, dexmedetomidine and lidocaine, which can all be used as adjuvants or substitutes for opioids during anesthesia (Kremer & Griffis, 2018; Mauermann et al., 2017). If the concept of opioid-free anesthesia is to be widely implemented in Sweden, more education about these drugs may be needed. As the nurse anesthetists are responsible for all the drugs they administer during anesthesia, including a dose assessment, extensive knowledge is needed about the pharmacodynamic effects of these non-opioid drugs (HSLF-FS 2017:37). Evidence-based practice should seek to understand the best combinations of non-opioid drugs and validate them for wide implementation of opioid-free anesthesia regimes of care (Johansson & Wallin, 2013; Walker & Avant, 2019).

Measuring the depth of anesthesia

The Swedish and American respondents had a completely different opinion on the importance of measuring depth of anesthesia during general anesthetics: more than two-thirds of the Swedish respondents answered *yes* to the question, while more than two-thirds of the American respondents answered *no* (figure 6). However, a higher percentage of the American respondents thought it was important to measure depth of anesthesia during opioid-free anesthesia, than in all general anesthetics, although the questions are not mutually exclusive (figure 7). Interestingly, the highest percentage of *I don't know*-answers from the American respondents regarded measuring depth of anesthesia in opioid-free anesthesia (11%). Compared to the percentages of Swedish *I don't know*-answers on many of the survey questions, this was not notably high, but isolated it showed the highest amount of uncertainty from the American respondents. Ketamine, one of the most popular drugs to be included in an opioid-free anesthesia regime of care (appendix 5, figure 13), is known to make BIS-monitoring less accurate because it targets NMDA receptors instead of $GABA_A$ (Rani & Harsoor, 2012). This could explain the increased American uncertainty about depth of anesthesia monitoring in opioid-free anesthesia. To be able to measure depth of anesthesia, in order to ensure adequate hypnosis and analgesia, new methods need to be developed and tested for opioid-free anesthesia using evidence-based practice. Guedel's classification of ether anesthesia, as well as the PRST-score, already less relevant today than at their introduction, may be rendered even more obsolete with the rise of opioid-free alternatives. As heart rate, blood pressure and cerebral neurotransmitters are affected differently by different non-opioid drugs, a complex multiparameter approach may be needed, combining measurements such as heart rate and blood pressure variation, EEG and skin conductance (Lavand'homme & Estebe, 2018). On the other hand, these questions can also be related to the question about risks of opioid-free anesthesia compared to traditional opioid-based anesthesia, where awareness was one of the risks with the most disagreement from American

respondents, consequently meaning it was perceived as an uncommon risk in opioid-free anesthesia (figure 5).

Opioid addiction

Opioid overdose is the leading cause of accidental death in the United States, and the government calls this opioid epidemic a national health emergency (Koepke et al., 2018; Kremer & Griffis, 2018). This was reflected in the present study, with more than 90% of the American respondents agreeing to the statement that opioid addiction is a major problem in society (figure 8). The Swedish respondents were generally less inclined to agree with the same statement. Not only was the aggregated agreement (agree + strongly agree) smaller, but also the intensity of the agreement differed largely from the American respondents: Only 27% of the Swedish respondents strongly agreed to the statement, versus 72% of the American respondents. This may partially be explained by the fact that, at least when looking at opioid prescription, no “epidemic” is seen in Sweden, as the prescription of opioids has been relatively constant during the last 10 years (Bäckryd, Heilig, & Hoffmann, 2017-05-03). However, the American opioid epidemic encompasses more than prescription drugs. Therefore, looking solely at prescription of opioids may not be enough to fully assess the situation, and statistics such as opioid overdose as cause of death should also be included. Looking at numbers from 2017, death from opioid overdose was 2.4 times as common in the United States than in Sweden, although the scope of the problem is growing in both nations (National Institute on Drug Abuse, 2019; Public Health Agency of Sweden, 2019).

Opioid-free anesthesia does not always lead to a totally opioid-free postoperative care. As described by Brandal et al. (2017), patients were prescribed opioids at discharge independently of patient assessed pain score and postoperative opioid consumption. This means that the attitude of the nurse anesthetist may also have a role in the extent of the use of opioids. An attempt to measure the attitudes of the nurse anesthetists towards opioids was made in the present study, by asking the questions presented in figures 8, 9 and 10. Although a majority of the American respondents believed that administering opioids intraoperatively can lead to opioid dependence, the answers were widely spread across the Likert scale (figure 10). In Sweden, the respondents were more inclined to disagree with the statement.

Although we have not found definitive evidence in scientific articles supporting the statement that administering opioids intraoperatively can lead to opioid dependence, a connection can be observed. Patients receiving high doses of remifentanil intraoperatively have a high risk of developing opioid-induced hyperalgesia, leading to increased postoperative pain and opioid consumption (Santonocito et al., 2018), thus increasing the risk of dependence (Brandal et al., 2017). Koepke et al. (2018) describe several studies where postoperative opioid dependence was developed in between 6% and 10% of patients after opioid-based anesthesia. A dose-dependent connection between intraoperative opioids and readmission to a hospital after anesthesia has also been observed (Long et al., 2018). We therefore consider that it may be

possible to conclude that administering opioids intraoperatively can lead to opioid dependence, although more evidence is needed to be certain.

Experiences of the investigators

The investigators participated in a two-week Student Exchange Program with the University of North Florida in the United States. The main purpose of the exchange program was to collect data for this study. We also visited a hospital in North Florida, where we observed local anesthesia practice. Although we did not have the opportunity to observe a patient under opioid-free anesthesia, most of the nurse anesthetist we met spoke highly of the concept. We made the observation that American nurse anesthetists generally used a more multimodal approach to anesthesia than we were accustomed to from our Swedish clinical placements. Drugs commonly used included midazolam, propofol, fentanyl, ketamine, lidocaine and dexmedetomidine.

Summary and clinical implications

Familiarity with opioid-free anesthesia was a lot more common in the United States than in Sweden (figures 2 and 3). Currently, only two Swedish anesthesia clinics administer opioid-free anesthesia and the knowledge of the concept is limited. This means that people who would benefit from opioid-free anesthesia, for reasons such as high risk of PONV or history of opioid abuse (figure 9 and appendix 5, figure 11), are less likely to avoid opioids during anesthesia in Sweden. Consequently, the Swedish healthcare system struggles with the negative effects of opioids in the postoperative patient care. Remifentanil, one of the most common intraoperative opioids used in Swedish anesthesia practice, causes hyperalgesia and increased postoperative opioid consumption (Santonocito et al., 2018). Ultimately, this may lead to increased opioid dependence, addiction and overdose in society, similarly to the opioid epidemic endured in the United States. With consequences of longer hospital stays and human suffering, both the economic and social sustainability of increased opioid consumption can be thoroughly questioned.

As awareness of the American opioid epidemic increases internationally, measures to prevent opioid consumption may be taken. Soon, patients may start to request opioid-free anesthesia, and Swedish healthcare practitioners need to prepare for the new paradigm by seeking evidence-based knowledge about the concept. Familiarity with non-opioid analgesics must be acquired for administration of safe anesthesia. Further understanding about the complexity of nociception during anesthesia may also be needed, to shift focus from relieving “pain“ with opioids, to other methods of suppressing the sympathetic response of surgical stimuli.

If, or when, opioid-free anesthesia becomes the norm, current methods of risk assessment and depth of anesthesia monitoring may become unreliable. Opioid-free anesthesia is a relatively new concept, and as an inexperienced practitioner, finding the right depth of anesthesia with a new combination of drugs may prove difficult. More research on opioid-free anesthesia, combinations and doses of non-opioid analgesics is needed, and RCTs should be systematically compiled in meta-analyses to determine the best available evidence-based

practice. In addition, the nursing perspective of opioid-free anesthesia should be researched using both qualitative and quantitative methods.

Conclusion

By having constructed, distributed and analyzed the responses of two web-based surveys, we have compared experiences of opioid-free anesthesia among nurse anesthetists in Sweden and the United States. We conclude that American nurse anesthetists have more clinical experience and theoretical knowledge of opioid-free anesthesia compared to Swedish nurse anesthetists. American nurse anesthetists experience many benefits of opioid-free anesthesia compared to traditional opioid-based anesthesia, while not experiencing many risks. Swedish nurse anesthetists have limited experience with opioid-free anesthesia, and are unsure about its risks and benefits. More education about non-opioid analgesics is needed for a safe implementation of the concept in Sweden. Nurse anesthetists in both nations think opioid addiction is a major problem in society, but American nurse anesthetists are more inclined to connect this problem to intraoperative opioids.

Our findings can be used to educate Swedish nurse anesthetists about opioid-free anesthesia, while hopefully stimulating further reading of evidence-based knowledge about the concept. We have also shown that the American nurse anesthetists' experiences with the benefits of opioid-free anesthesia correspond with the Swedish nurse anesthetists' priorities in all perioperative patient care. This suggests that opioid-free anesthesia would be beneficial to postoperative patient outcome, if implemented widely in Sweden.

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Appendix 1: Survey (English version)

Opioid Free Anesthesia in Sweden and Florida (English version)

The survey has been approved by the Human Subjects Ethics process at the University of Gothenburg, Sweden. You are free to participate, or not, as you decide. A decision not to participate will not disadvantage you in any way. Completion of the survey indicates your consent to participate.

No personal data, or HPI is collected. All data will be aggregated and de-identified. The principal investigators are Daniel Verbeeck, BSN, RN and Sofia Pihlblad, BSN, RN, nurse anesthesiology students at the Sahlgrenska Academy, University of Gothenburg. If you have any questions, please call (+[redacted]) Dr. John McDonough at any time.

1. **1. Gender:**
   Markera endast en oval.
   - ◯ Female
   - ◯ Male

2. **2. Year of birth:**

   _____

3. **3. I am a ...**
   Markera endast en oval.
   - ◯ CRNA
   - ◯ SRNA

4. **4. If you are a CRNA, how long have you been practicing?**
   Markera endast en oval.
   - ◯ 0-2 years
   - ◯ 3-5 years
   - ◯ 6-10 years
   - ◯ 11-15 years
   - ◯ more than 16 years
   - ◯ I am an SRNA

5. **5. In which country do you practice?**
   Markera endast en oval.
   - ◯ United States
   - ◯ Sweden

6. **6. In what hospital do you practice?**
Markera endast en oval.

- ◯ Hospital in the United States

7. **7. I am familiar with the concept of "opioid free anesthesia" (OFA)**
Markera endast en oval per rad.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
-	◯	◯	◯	◯	◯

8. **8. I obtained my knowledge about OFA from:**
Markera alla som gäller.

- ☐ University lectures
- ☐ Lectures at my work place
- ☐ Scientific articles
- ☐ Clinical practice: at least once a week
- ☐ Clinical practice: at least once a month
- ☐ Clinical practice: at least once a year
- ☐ Other
- ☐ I have no knowledge about OFA

9. **9. In my opinion, the evidence supports the use of OFA**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
-	◯	◯	◯	◯	◯	◯

10. **10. In my opinon, OFA has benefits, or positive effects, compared to traditional opioid anesthesia, related to**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Patients' desires	◯	◯	◯	◯	◯	◯
Rapid awakening from anesthesia	◯	◯	◯	◯	◯	◯
Risk of PONV	◯	◯	◯	◯	◯	◯
Post operative pain	◯	◯	◯	◯	◯	◯
Avoiding delay of oral intake of food/fluids	◯	◯	◯	◯	◯	◯
Early ambulation	◯	◯	◯	◯	◯	◯
Avoiding urinary retention	◯	◯	◯	◯	◯	◯
Avoiding constipation	◯	◯	◯	◯	◯	◯
Avoiding impaired cognitive function	◯	◯	◯	◯	◯	◯

11. **11. In my opinon, OFA has risks, or negative effects, compared to traditional opioid anesthesia, related to intraoperative**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Heart rate: too high						
Heart rate: too low						
Blood pressure: too high						
Blood pressure: too low						
Awareness						
Delay of spontaneous breathing						

12. **12. The following drugs should be included in an OFA regime of care:**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Ketamine						
Lidocaine						
Propofol						
Dexmedetomidine						
Clonidine						
Magnesium						
Ketorolac						
Ibuprophen						
Acetaminophen / Paracetamol						
Nitrous oxide						

13. **13. I am familiar with the use of the following drugs:**
Markera endast en oval per rad.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Ketamine					
Lidocaine					
Propofol					
Dexmedetomidine					
Clonidine					
Magnesium					
Ketorolac					
Ibuprophen					
Acetaminophen / Paracetamol					
Nitrous oxide					

14. **14. Do you think it is important to measure depth of anesthesia in OFA general anesthetics?**
Markera endast en oval.

- ◯ Yes
- ◯ No
- ◯ I don't know

15. **15. Do you think it is important to measure depth of anesthesia in all general anesthetics?**
Markera endast en oval.

- ◯ Yes
- ◯ No

16. **16. If you answered "yes" to #15, do you do it**
Markera endast en oval.

- ◯ Always
- ◯ When a monitor is available
- ◯ Only for patients "at risk"
- ◯ Only in general anesthesia with muscle relaxants
- ◯ Rarely or never

17. **17. In my opinon, OFA should be used for patients who have a history of opioid abuse / dependence**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
-	◯	◯	◯	◯	◯	◯

18. **18. In my opinon, opioid dependence is a major problem in our society**
Markera endast en oval per rad.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
-	◯	◯	◯	◯	◯

19. **19. I believe administering opioids intraoperatively can lead to opioid dependence**
Markera endast en oval per rad.

	I don't know	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
-	◯	◯	◯	◯	◯	◯

20. **20. In my opinon, the following things are important to avoid in all anesthesia practice**
Markera endast en oval per rad.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Delayed awakening from anesthesia					
PONV					
Post operative pain					
Delay in oral intake of food/fluids					
Delay in ambulation					
Urinary retention					
Constipation					
Impaired cognitive function					

Appendix 2: Survey (Swedish version)

Opioidfri anestesi i Sverige och USA (Svensk version)

Att delta i studien är frivilligt. Genom att besvara enkäten och trycka på skicka samtycker du till att delta i studien.

Endast de svar som du själv väljer att lämna in kommer att registreras. All data kommer att redovisas på gruppnivå och avidentifieras. Enkäten är anonym och dina svar kommer inte att kunna härledas till dig. Information om vem som har svarat på enkäten registreras ej. Dina svar kommer att behandlas så att inte obehöriga kan ta del av dem.

1. **1. Är du kvinna eller man?**
   Markera endast en oval.
   - ◯ Kvinna
   - ◯ Man

2. **2. Vilket år är du född?**

   _____

3. **3. Jag är...**
   Markera endast en oval.
   - ◯ Anestesisjuksköterska
   - ◯ Anestesisjuksköterskestudent

4. **4. Om du är anestesisjuksköterska, hur lång tid har du arbetat inom anestesi?**
   Markera endast en oval.
   - ◯ 0-2 år
   - ◯ 3-5 år
   - ◯ 6-10 år
   - ◯ 11-15 år
   - ◯ mer än 16 år
   - ◯ Jag är anestesisjuksköterskestudent

5. **5. I vilket land arbetar du?**
   Markera endast en oval.
   - ◯ USA
   - ◯ Sverige

6. **6. I vilken sorts sjukhus arbetar du?**
Markera endast en oval.

- ◯ Universitetssjukhus
- ◯ Länssjukhus
- ◯ Sjukhus/Lasarett

7. **7. Jag känner till konceptet "opioidfri anestesi" (OFA)**
Markera endast en oval per rad.

	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
-	◯	◯	◯	◯	◯

8. **8. Jag har fått kunskap om OFA genom:**
Markera alla som gäller.

- ☐ Föreläsningar vid universitet
- ☐ Föreläsningar på min arbetsplats
- ☐ Vetenskapliga artiklar
- ☐ Kliniskt utförande: minst en gång i veckan
- ☐ Kliniskt utförande: minst en gång i månaden
- ☐ Kliniskt utförande: minst en gång om året
- ☐ Annat
- ☐ Jag har ingen kunskap om OFA

9. **9. Jag anser att det finns evidens som stödjer användningen av OFA**
Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
-	◯	◯	◯	◯	◯	◯

10. **10. Jag anser att OFA har fördelar, eller positiva effekter, jämfört med traditionell opioidanestesi, relaterat till**

Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
Patientens önskemål						
Snabbt uppvaknande från anestesi						
Risk för PONV						
Postoperativ smärta						
Undvikande av fördröjt oralt intag av vätska/mat						
Tidig mobilisering						
Undvikande av urinretention						
Undvikande av förstoppning						
Undvikande av nedsatt kognitiv funktion						

11. **11. Jag anser att OFA har risker, eller negativa effekter, jämfört med traditionell opioidanestesi, relaterat till intraoperativ**

Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
Hjärtfrekvens: för hög						
Hjärtfrekvens: för låg						
Blodtryck: för högt						
Blodtryck: för lågt						
Awareness						
Fördröjd spontanandning						

12. **12. Följande läkemedel bör inkluderas i en OFA-vårdplan:**

Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
Ketamin						
Lidokain						
Propofol						
Dexmedetomidin (Dexdor)						
Klonidin (Catapresan)						
Magnesium						
Ketorolak (Toradol)						
Ibuprofen						
Paracetamol						
Lustgas (N2O)						

13. **13. Jag känner mig förtrogen med att använda följande läkemedel:**
Markera endast en oval per rad.

	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
Ketamin	◯	◯	◯	◯	◯
Lidokain	◯	◯	◯	◯	◯
Propofol	◯	◯	◯	◯	◯
Dexmedetomidin (Dexdor)	◯	◯	◯	◯	◯
Klonidin (Catapresan)	◯	◯	◯	◯	◯
Magnesium	◯	◯	◯	◯	◯
Ketorolak (Toradol)	◯	◯	◯	◯	◯
Ibuprofen	◯	◯	◯	◯	◯
Paracetamol	◯	◯	◯	◯	◯
Lustgas (N2O)	◯	◯	◯	◯	◯

14. **14. Tycker du att det är viktigt att mäta anestesidjup vid OFA generell anestesi?**
Markera endast en oval.

- ◯ Ja
- ◯ Nej
- ◯ Vet ej

15. **15. Tycker du att det är viktigt att mäta anestesidjup vid all generell anestesi?**
Markera endast en oval.

- ◯ Ja
- ◯ Nej

16. **16. Om du svarade ja på fråga 15, gör du det**
Markera endast en oval.

- ◯ Alltid
- ◯ När apparat är tillgänglig
- ◯ Enbart för riskpatienter
- ◯ Endast vid generell anestesi med muskelrelaxantia
- ◯ Sällan eller aldrig

17. **17. Jag anser att OFA bör användas för patienter som har en historik av opioidmissbruk / -beroende**
Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
-	◯	◯	◯	◯	◯	◯

18. **18. Jag anser att opioidberoende är ett stort problem i vårt samhälle**
Markera endast en oval per rad.

	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
-					

19. **19. Jag tror att intraoperativ administration av opioider kan leda till opioidberoende**
Markera endast en oval per rad.

	Vet ej	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
-						

20. **20. Jag anser att följande punkter är viktiga att undvika vid all anestesi**
Markera endast en oval per rad.

	Instämmer inte alls	Instämmer inte	Varken eller	Instämmer	Instämmer helt
Fördröjt uppvaknande från anestesi					
PONV					
Postoperativ smärta					
Fördröjt oralt intag av vätska/mat					
Fördröjd mobilisering					
Urinretention					
Förstoppning					
Nedsatt kognitiv funktion					

Appendix 3: Information to the research participants

Forskningspersonsinformation – Opioidfri anestesi i Sverige och USA

Bakgrund
Denna studie avser att jämföra svenska och amerikanska anestesisjuksköterskors upplevelser och erfarenheter av opioidfri anestesi. Studien utförs av två studenter på specialistsjuksköterskeprogrammet med inriktning mot anestesisjukvård vid Göteborgs universitet.

Förfrågan om deltagande
Du är inbjuden att delta i den här studien för att du arbetar som anestesisjuksköterska i Sverige eller i USA, eller för att du studerar till anestesisjuksköterska. Vi är intresserade av dina erfarenheter av opioidfri anestesi (OFA). Att delta i studien är frivilligt. Valet att inte delta kommer inte att leda till några negativa följder. Enkäten har skickats ut per email från våra kontaktpersoner; Dr. John McDonough, University of North Florida och Dr. Pether Jildenstål, Göteborgs universitet. Forskningshuvudman för projektet är Göteborgs universitet.

Hur går studien till?
Som forskningsperson kommer du att få svara på en elektronisk enkät. En länk till enkäten kommer skickas till din e-post. Enkäten består av 20 flervalsfrågor där du har möjligheten att bedöma din erfarenhet och upplevelse på skalor. Att besvara enkäten tar ca 5-10 minuter.

Resultatet kommer att analyseras statistiskt genom att jämföra svar från Sverige och USA. Enkäterna innehåller samma frågor, endast översatta till svenska eller engelska.

Fördelar och risker med deltagande
Denna studie kommer inte att ge några direkta fördelar för dig, men förhoppningen är att erfarenhet av opioidfri anestesi i Sverige och USA kommer kunna jämföras, spridas och utbytas mellan anestesisjuksköterskor i båda länder. Om någon fråga får dig att känna dig obekväm kan du lämna frågan obesvarad.

Hantering av data och sekretess
Endast de svar som du själv väljer att lämna in kommer att registreras. All data kommer att redovisas på gruppnivå och avidentifieras. Enkäten är anonym och dina svar kommer inte att kunna härledas till dig. Information om vem som har svarat på enkäten registreras ej. Dina svar kommer att behandlas så att inte obehöriga kan ta del av dem. Ansvarig för dina personuppgifter är Göteborgs Universitet. Dataskyddsombud: Kristina Ullgren (dataskydd@gu.se).

Hur fås information om studiens resultat?
Svarsdata som samlas in kommer att användas i en Magisteruppsats som skrivs i Specialistsjuksköterskeprogrammet med inriktning mot anestesisjukvård vid Göteborgs universitet. Uppsatsen kommer att publiceras i GUPEA, Göteborgs universitets elektroniska arkiv (gupea.ub.gu.se) och kan fritt laddas ner där. Uppsatsen kan bli publicerad i en

vetenskaplig tidskrift. Du kan också kontakta de huvudansvariga forskarna för att få en elektronisk kopia.

Försäkring och ersättning
Studien är inte kopplad till något försäkringsskydd. Ersättning för deltagande utgår ej. Du förväntas inte få några utgifter eller förlorad inkomst på grund av ditt deltagande.

Frivillighet
Att delta i studien är frivilligt. Genom att besvara enkäten och trycka på skicka samtycker du till att delta i studien. Du har rätt att när som helst under besvarandet av enkäten ångra dig och avbryta studien utan att ge någon motivering. De forskningsdata som du har bidragit med kommer då att uteslutas och all svarsdata kommer att raderas.

Kontaktinformation
Huvudansvariga forskare är:
Daniel Verbeeck, BSN, leg. sjuksköterska. E-post: gusverbda@student.gu.se
Sofia Pihlblad, BSN, leg. sjuksköterska. E-post: guspihlb@student.gu.se

Kontakt på University of North Florida:
Dr. John P. McDonough
CRNA, EdD, Dr.(habil)NScA, APRN, FRSM
Professor & Director, Nurse Anesthesiology Program

Forskningshuvudman samt personuppgiftsansvarig för studien är Göteborgs Universitet.
Pether Jildenstål
Programansvarig specialistsjuksköterskeutbildningen,
Universitetslektor, Docent, Medicine doktor
Översjuksköterska i anestesi, an/op/iva kliniken, område 5, SU, Göteborg
Institutionen för vårdvetenskap och hälsa
Sahlgrenska akademin vid Göteborgs Universitet
Arvid Wallgrensbacke
Box 457
405 30 Göteborg, besöksadress 413 46, Göteborg
Tfn: +46317866044
E-post: pether.jildenstal@gu.se

Appendix 4: Non-opioid drugs

Ketamine

Ketamine is an NMDA receptor antagonist with analgesic, anti-hyperalgesic, anesthetic and sedative effects. By depressing activity in the cortex and simultaneously stimulating the limbic system, ketamine creates so-called dissociative anesthesia. This is associated with vivid dreams and hallucinations. Ketamine can also be used to treat acute pain, treat and prevent chronic pain, while even small doses significantly reduce opioid need. Some side effects are related to increased epinephrine and norepinephrine circulation, leading to tachycardia and hypertension, while other side effects include increased intracerebral pressure, salivation and muscle tone, and bronchial dilatation (Bekhit et al., 2015). In a meta-analysis hypothesizing that ketamine provides better hemodynamic control than placebo, ketamine was found to have a significantly reduced effect on blood pressure variability, but no such effect on heart rate (Forget & Cata, 2017).

Lidocaine

Lidocaine is an amino amide that is used as a local anesthetic, blocking sodium channels and thereby inhibiting the neural action potential (Bekhit et al., 2015). However, it can also be used intravenously for a number of purposes. It was initially used intravenously for its antiarrhythmic properties, but it also has analgesic, anti-hyperalgesic, anti-inflammatory, anti-microbial and anti-tumoral effects, as well as preventing bronchoconstriction and postoperative ileus. Even intravenously, at recommended doses, therapeutic index is high and concentration stays well below toxic levels (Beaussier, Delbos, Maurice-Szamburski, Ecoffey, & Mercadal, 2018).

Propofol

Propofol is one of our most common intravenous induction drugs. Propofol is prepared in a fat emulsion and similarly to barbiturates binds to the $GABA_A$ receptor. Negative inotropy and peripheral vasodilatation commonly occurs during induction with profound decreases in blood pressure (Hirsch et al., 2015).

Alpha 2-agonists

The drugs clonidine and dexmedetomidine are both alpha 2-agonists that can be used as adjuvants for analgesic purposes. They work through stimulating alpha 2-receptors, which leads to decreased release of norepinephrine peripherally and in the CNS. The effect is both analgesic and sedative, without causing respiratory depression. The drugs can be used to reduce both opioid consumption and the incidence of nausea. Side effects can be bradycardia and hypotension (Bekhit et al., 2015; Santonocito et al., 2018).

Magnesium

Magnesium sulfate is used as an antiarrhythmic drug which affects the myocardial cells. It also has an analgesic effect, likely explained by its ability to block NMDA-receptors. Magnesium can be used as a compliment to the anesthesia regime intravenously, intrathecally, epidurally or through skin infiltration. In clinical trials, intravenous magnesium reduced the need for opioids by as much as 24%. Magnesium lowers the heart rate, but not the blood pressure. At high serum levels, side effects include neuromuscular blockade, skeletal muscle weakness, lethargy, nausea, vomiting and electrocardiogram changes (Bekhit et al., 2015). In a meta-analysis, magnesium was found to stabilize heart rate. Magnesium can be used as an adjuvant analgesic in opioid-free anesthesia, and also maintains hemodynamic stability when used in combination with ketamine (Forget & Cata, 2017).

COX-inhibitors

Ketorolac (Toradol®) and ibuprofen are nonsteroidal anti-inflammatory drugs (NSAIDs), also known as COX-inhibitors. Inhibition of COX-2 has analgesic effects, while inhibition of COX-1 inhibits platelet aggregation and prostaglandin synthesis in the gastric mucosa. Both ketorolac and ibuprofen are non-selective COX-inhibitors, meaning they affect both COX-1 and COX-2 (Bekhit et al., 2015). These drugs are mainly administered intraoperatively to reduce postoperative pain.

Acetaminophen / Paracetamol

Paracetamol has both analgesic and antipyretic effects and can be used as a basis for postoperative analgesia. The exact pharmacodynamic mechanism is not known, it is believed to involve both peripheral and central effects. Paracetamol is metabolized in the liver and overdoses can cause irreversible hepatic injury. However, within therapeutic doses, paracetamol has no side effects and is also suitable for pregnant women and children (FASS, 2018a).

Nitrous oxide (N_2O)

Nitrous oxide causes sleep and analgesia. It is the oldest anesthetic agent still in use, discovered in 1772. Nitrous oxide has a high MAC-value, meaning it can only be used as a complementary anesthetic, though it has an additive and potentiating effect on other anesthetic gases leading to a dose reduction. It is excellent to use during induction, as it causes negligible respiratory depression and is nearly odorless in concert with being hemodynamically stable. Nitrous oxide diffuses into air-filled cavities in the body, such as the middle ear, sinuses and gas filled bowels as well as the cuff of an endotracheal tube. Hence it is contraindicated for ileus, open eye or skull trauma, pneumothorax and surgery in the middle ear (Frost, 2015; Ko, Kaye, & Urman, 2015).

Appendix 5: Charts

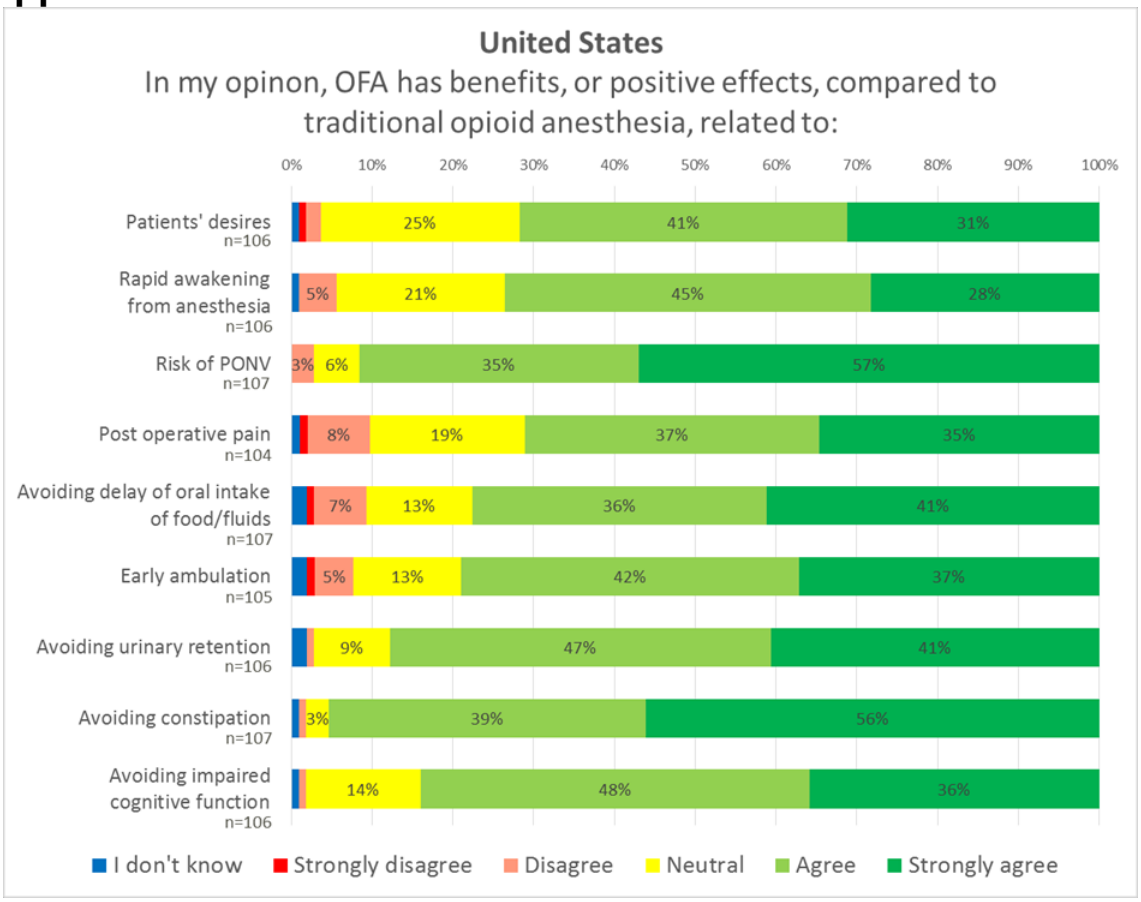

Figure 11. Benefits of opioid-free anesthesia according to American nurse anesthetists. (n= see figure)

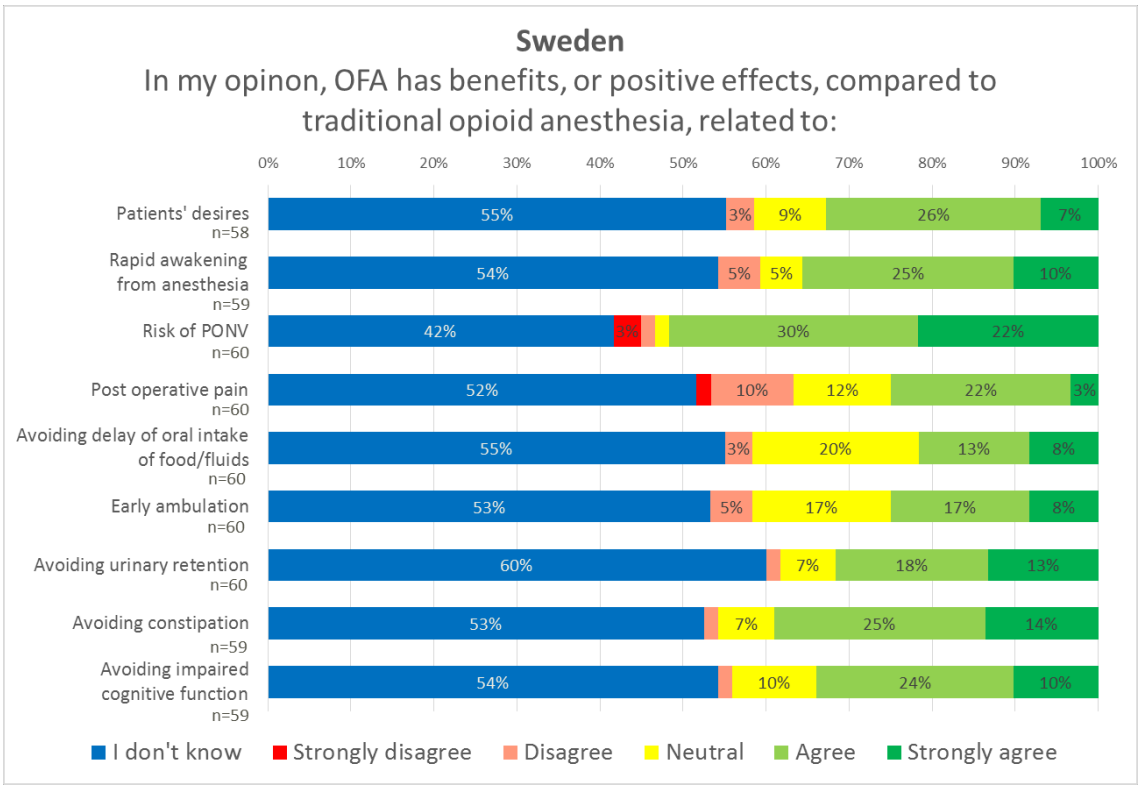

Figure 12. Benefits of opioid-free anesthesia according to Swedish nurse anesthetists. (n= see figure)

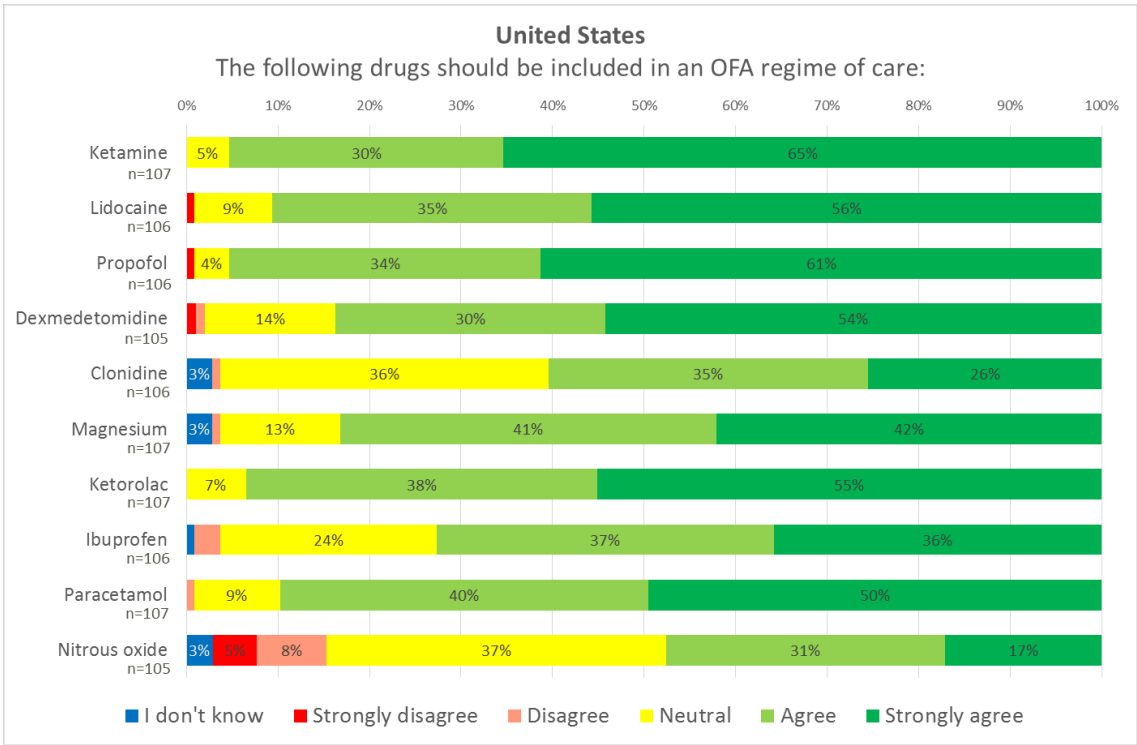

Figure 13. Drugs to be included in an opioid-free anesthesia regime of care. Answers from the United States. (n= see figure)

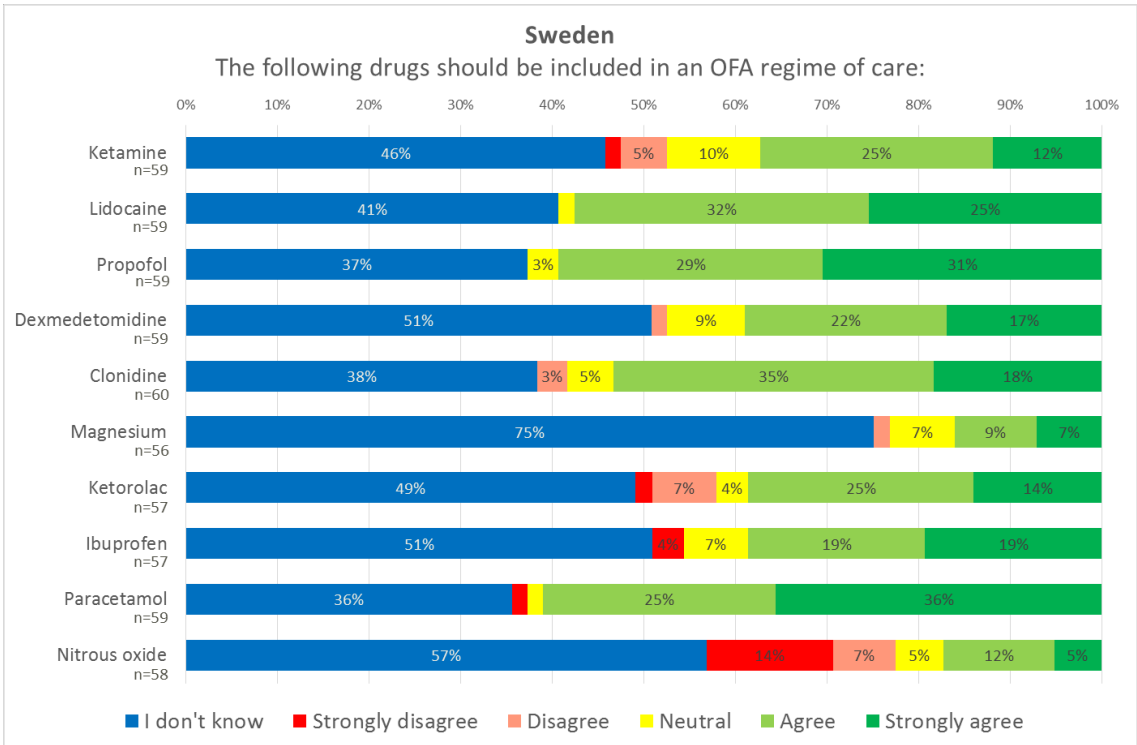

Figure 14. Drugs to be included in an opioid-free anesthesia regime of care. Answers from Sweden. (n= see figure)

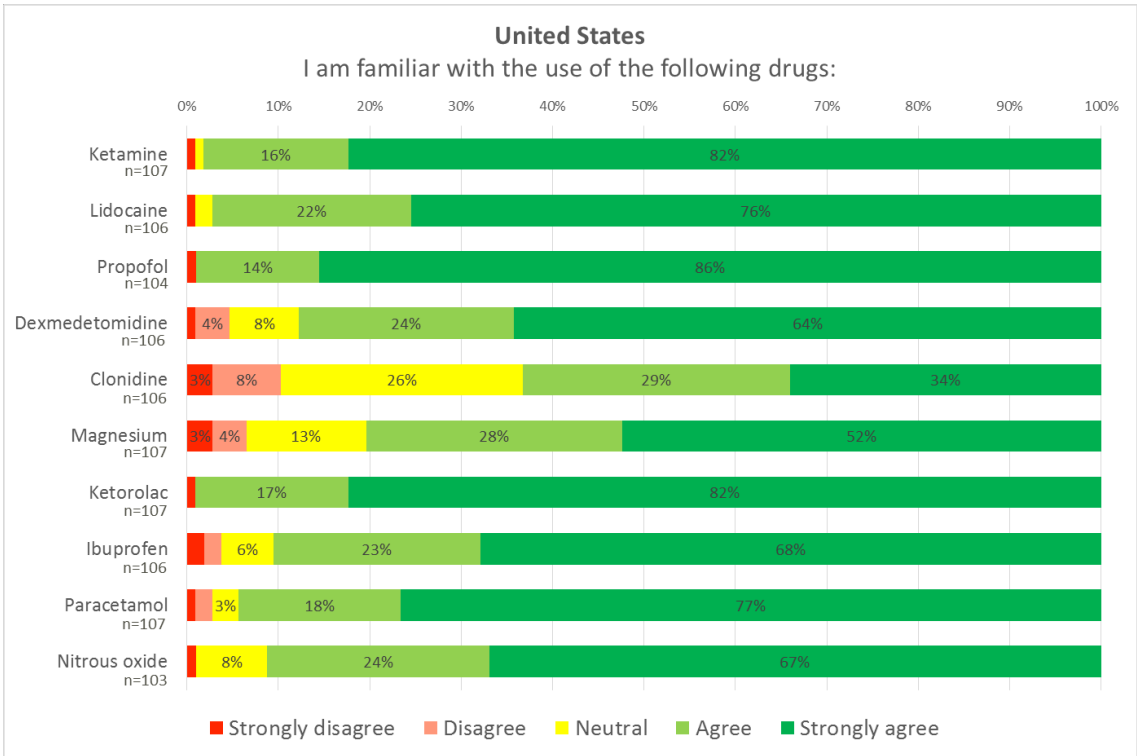

Figure 15. Self-reported familiarity with non-opioid drugs. Answers from the United States. (n=see figure)

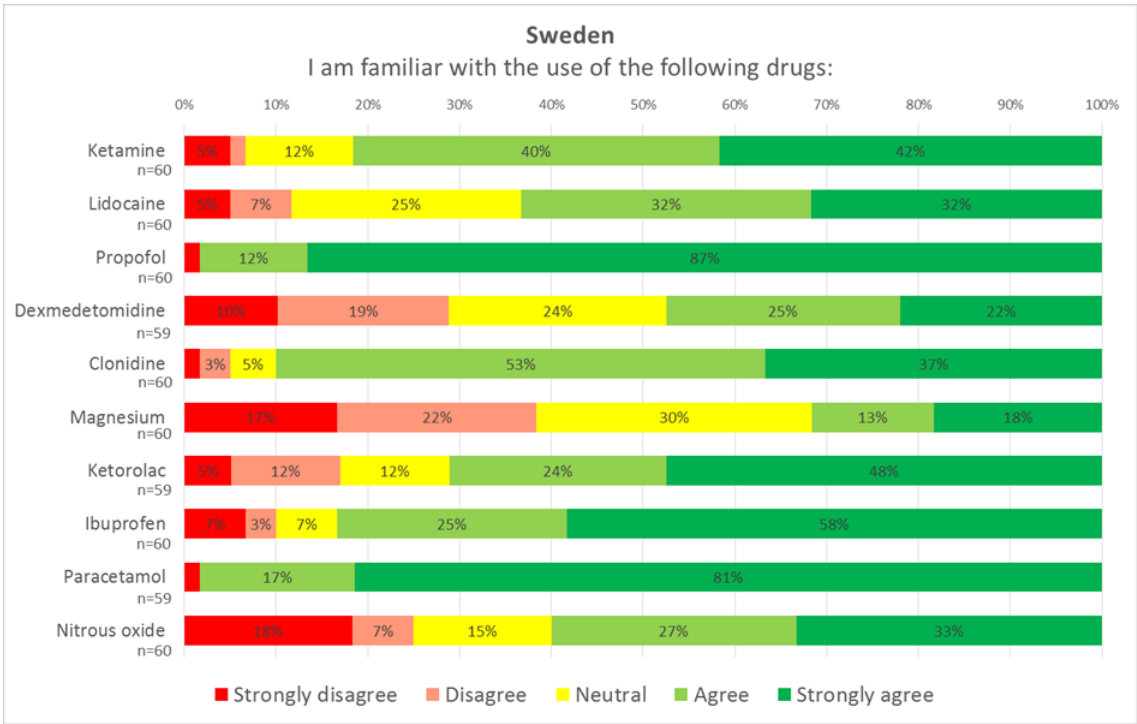

Figure 16. Self-reported familiarity with non-opioid drugs. Answers from Sweden. (n=see figure)

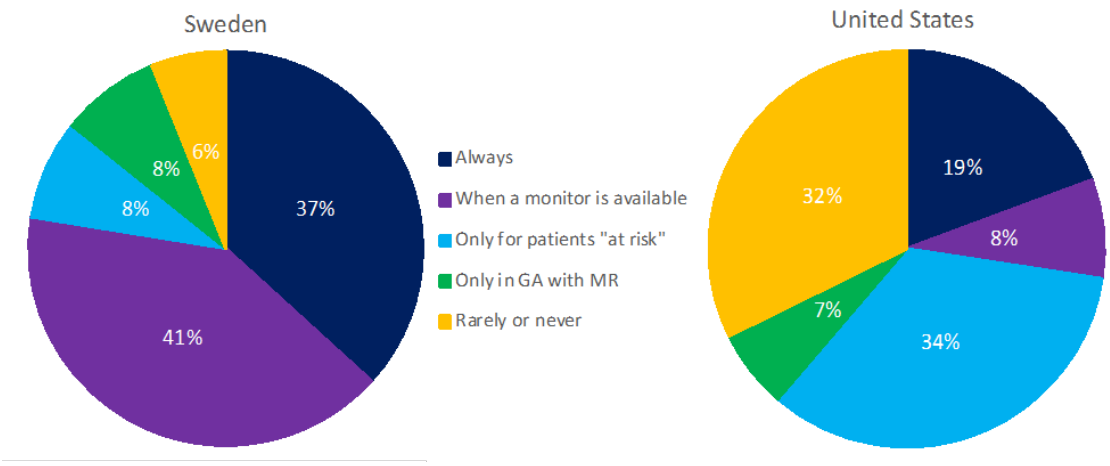

Figure 17. When depth of anesthesia is measured. “If you answered ‘yes’ to ‘Do you think it is important to measure depth of anesthesia in all general anesthetics?’ do you do it” (Sweden n=49, United States n=62; GA=general anesthesia, MR=muscle relaxants.)

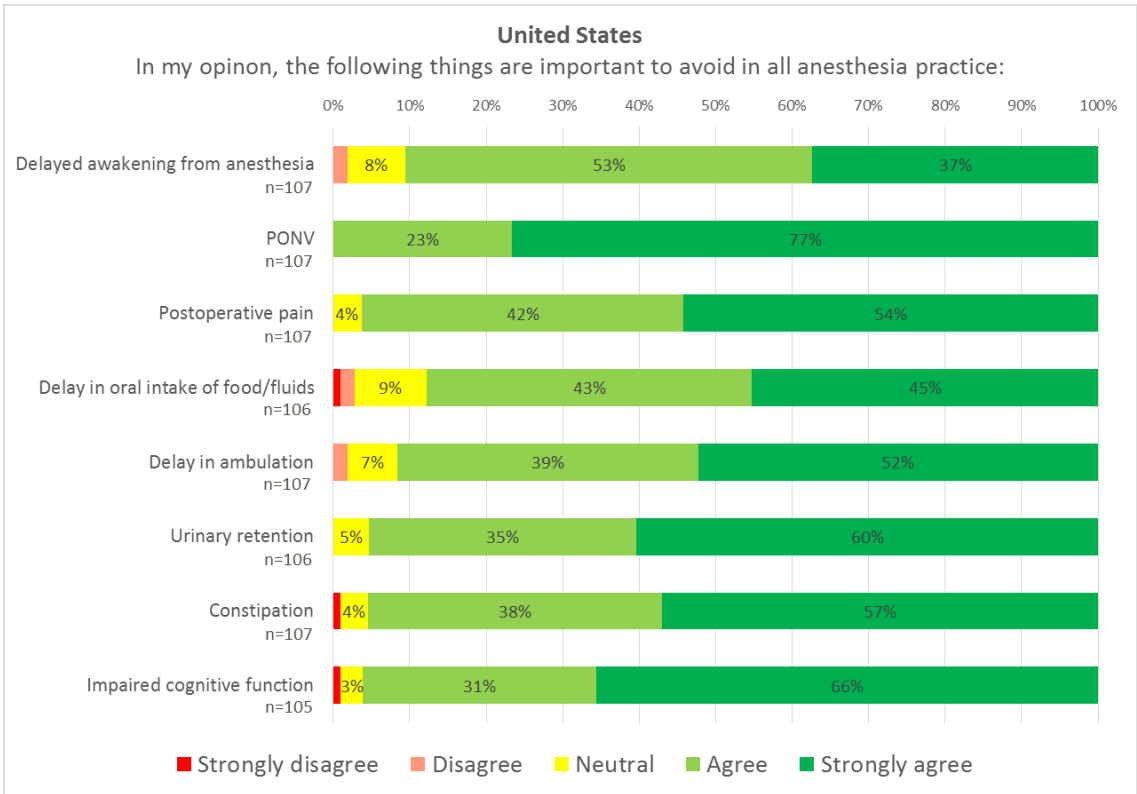

Figure 18. Important to avoid in all anesthesia according to American nurse anesthetists. (n=see figure)

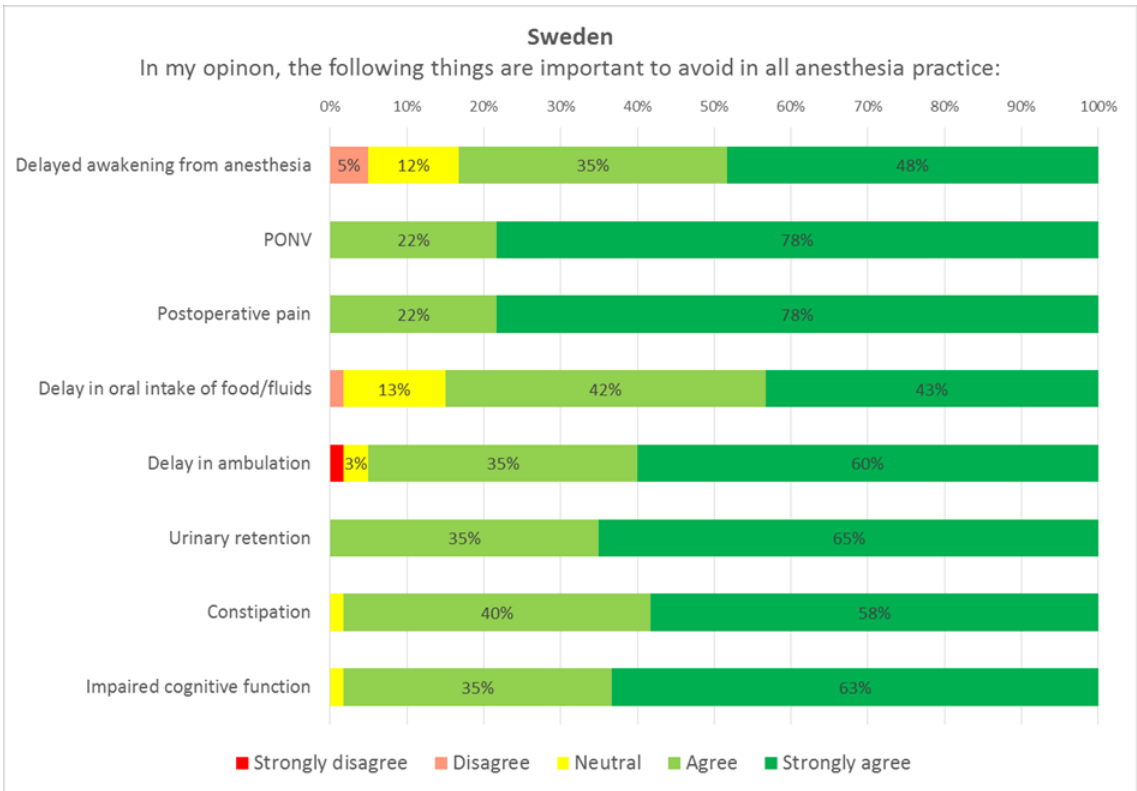

Figure 19. Important to avoid in all anesthesia according to Swedish nurse anesthetists. (n=60)