RECOVERY TIMES AND ADVERSE EVENTS BETWEEN PROPOFOL AND MIDAZOLAM DURING COLONOSCOPY

by

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Abstract

Sedation and analgesia are integral to successful colonoscopy completion and controversy surrounds the optimal pharmacokinetic agent that will target and maintain a moderate sedation level, offer operational efficiency with reduced recovery time, and minimize risk for cardiopulmonary complications. Current practice is imprecise; manual administration of procedural sedation using a combination of benzodiazepine and opioids puts patients at risk for descending into deeper levels of sedation, which can lead to risk for cardiorespiratory depression, and an increase in recovery times for up to two hours.

Studies have reported that propofol, a sedative agent with a short half life, can result in a shorter recovery, however there is limited research that has used consistent measurement to evaluate the procedural sedation recovery process or the influence of predictors such as age, sex, medication history, medical history, procedure time and body mass index (BMI), on recovery time and cardiopulmonary risk.

Therefore, a non-experimental descriptive retrospective study was undertaken with two groups of 100 subjects who had either midazolam administered manually or propofol administered using the Sedasys® System for colonoscopy to explore the differences in procedure length and recovery time between these groups.

Participants in the propofol group were somewhat younger and healthier than those in the midazolam group; average age 50.1 years versus 58.9 years, took fewer cardiac medications, had a lower BMI, and a lower incidence of cardiac or respiratory disease.

Multiple regression analyses were conducted to assess the contribution of independent clinical predictors (age, sex, BMI, medical history and medication history) for duration of recovery from procedural sedation and analgesia and the incidence of sedation-related

adverse events. Propofol provided the largest contribution to the variance in recovery time after controlling for other significant predictors (R-squared = 0.22). Based on the MOAA/S score, participants who received propofol were discharged home sooner than those who received midazolam. There were no adverse events in either group.

The results of this study suggest that propofol for procedural sedation during colonoscopy may improve efficiencies and throughput in the endoscopy suite and may provide a safe means that can assist in meeting the rising demand for colonoscopy.

Preface

This thesis is an original intellectual product of the author, Jennifer Switzer under the supervision of Dr. Leanne Currie. Information for this research was obtained from health records in a large surgical outpatient unit in an urban health authority in Canada following a trial comparing the effects of two sedation options (standard practice and a new sedative option) for patients undergoing colonoscopy between March and October of 2012. As the Clinical Nurse Educator in this facility, I coordinated training for nurses and physicians during the trial and abstracted data from patient charts retrospectively.

The aim of the research was to explore recovery times and sedation-related cardiopulmonary events between patients who had the standard sedation and those who had the new sedative option, while controlling for potential confounding variables: age, sex, BMI, medical history and procedure length.

Ethics approval was obtained from the Fraser Health Research Ethics Board (FHREB 2012-075) and the University of British Columbia, Clinical Research Ethics Board (H12-01206).

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Dedication

Although a passion for clinical practice and improved patients outcomes and a commitment and dedication to challenge my being were all fundamental in the completion of my graduate studies and thesis, it was the support of my family that I owe my greatest appreciation. To my husband's unfailing support as he took over every aspect of my day to day challenges so that I could focus solely on my studies; and to my children, their wives, fiancés and girlfriends for their encouragement, praise and patience throughout this journey.

Chapter 1: Introduction

Colorectal cancer is a leading cause of morbidity and mortality in the Western world, and in 2012 it was estimated that 22,200 Canadian men and women were diagnosed with this disease and of these, 9,200 died from the disease (Center, Jemal, & Ward, 2009; Colorectal Cancer Association of Canada (CCAC), 2012; Ferlay et al., 2010; Statistics Canada, 2012). Bowel cancer originates from a benign adenomatous polyp, and develops slowly; survival improves when these polyps are removed and disease is detected early (Brenner, Altenhofen, & Hoffmeister, 2010; Leddin et al., 2004; Lubarsky, Candiotti, & Harris, 2007). In the last 15 years there has been a significant increase in the number of colonoscopies performed, due in part to ageing of the world's population (Ferlay et al., 2010; Cohen et al., 2006; Safarty & Wender, 2007). Moreover, organized screening programs are being developed around the world and while this has led to an increase in the rate for colorectal cancer screening, it is placing a burden on available endoscopy resources (Leddin et al., 2004; Shabas, 2003).

Colonoscopy is the procedure of choice for screening and surveillance of colonic neoplasia and for diagnosing colonic disease because it is more sensitive than radiological imaging and offers the option for therapeutic intervention such as removal of polyps when warranted (Bowles et al., 2004; Canadian Partnership Against Cancer (CPAC), 2010; Rex et al., 2002). Colonoscopy is performed using a flexible colonoscope to evaluate the mucosal lining of the entire colon from the distal rectum to the cecum. During the procedure, the cecum can be recognized by visualization of the ileocecal valve (Ciroccu & Rusin, 1995). As the colonoscope is advanced through the colon, mesenteric stretching and colonic spasms often results in discomfort for the patient. When patients have difficulty tolerating the procedure, intubation to the cecum may be compromised, and the risk for missing adenomas

or adenocarcinomas in the colon is increased (Bell, 2002; Bressler et al., 2007; Radaeli, Meucci, Sgroi, & Minoli, 2008; Riphaus et al., 2009; Wang, Shen, Ziao, Xu, & Tang, 2011), therefore procedural sedation, via sedatives with or without analgesics, is used during the procedure.

Procedural sedation is intended to induce a depressed level of consciousness while allowing the patient to maintain oxygenation and independent airway control (Godwin et al., 2005). Procedural sedation is considered to be integral to the success of gastroenterology procedures, however the most suitable combination of drugs is still debated (Godwin et al., 2005; Sheta, 2010). Approximately 90% of patients receive sedatives and analgesics during colonoscopy. The remaining 10% elect to have the colonoscopy without sedatives or analgesics for a variety of reasons; they prefer to be able to communicate coherently with care providers during and after the procedure, they choose to avoid risk associated with sedative and analgesic agents, or they prefer to reduce the costs of the procedure (in countries other than Canada with private healthcare) (Cohen et al., 2006; Cohen et al., 2010; Metzner & Domino, 2010; Porostocky, Chiba, Colacino, Sadowski, & Singh, 2011). Although procedural sedation delays recovery and discharge and increases the risk of cardiopulmonary complications, the discomfort experienced during an colonoscopy in which patients are not sedated may result in a missed cancer due to the inability to visualize the entire colon and excessive discomfort resulting in non-compliance for subsequent colonoscopic follow up (Bressler et al., 2007; Cohen al., 2007; Cohen et al., 2010).

Currently there is no set standard procedural sedation regimen for gastrointestinal endoscopy procedures, however the minimal amount of sedation for the shortest duration needed to achieve visualization of the entire colon is recommended (Huang & Eisen, 2004;

Koshy, Nair, Norkus, Hertan, & Pitchumoni, 2000). Benzodiazepines and opioids are the drug classes most widely used for endoscopic sedation (Cohen et al., 2007). The most commonly used benzodiazepine is midazolam, and the most commonly used opioid is fentanyl (Triantafillidis, Merikas, Nikolakis, & Papalois, 2013). Antagonist agents are available for both of these medications; therefore if a patient becomes over-sedated the effects of the drugs can be reversed (Society for Gastroenterology Nurses and Associates, Inc., 2013; Cohen et al., 2007). Procedural sedation using a combination of benzodiazepines and opioids results in a residual tranquilizing effect for 30 minutes to 3 hours after the procedure (Cohen, Dubovsky, Aisenbert, & Miller, 2003); In the ambulatory setting, monitoring patients for 3 hours is a resource-intensive activity (Vargo, Bramley, Meyer, & Nightengale, 2007; Cohen et al., 2003). Furthermore, although mortality related to colonoscopy is relatively uncommon, procedural sedation has been implicated in colonoscopy-related deaths (Sarkar, Bowering, Azim, & Bodger, 2009; Triantafillidis et al., 2013). Therefore identification of innovative and efficient procedural sedation methodologies while not increasing patient risk is key to the sustainability of our health care system.

Individuals differ in their response to sedation. Physiological factors may increase sedation depth and subsequently length of recovery; Interactions with current medications or comorbid conditions involving abnormalities of major organ systems may result in altered drug metabolism, reduced drug clearance and cumulative sedation doses due to advancing age and associated decline in organ function. In addition, gender-related anatomical differences may result in difficult intubation and prolonged procedure time requiring larger

sedation/analgesia doses and prolonged recovery (Freire, Bassit, Chodhary, Piong, & Merchant, 2011; Kanonidou & Karystianou, 2007, Qureshi et al., 2006).

Propofol was initially developed and approved for induction and maintenance of anesthesia and as such, the drug can provide a deeper level of sedation than the combination of benzodiazepines/opioids used for procedural sedation. The propofol product label states the drug "should be administered only by persons trained in the administration of general anesthesia" (Cohen et al., 2007, p. 681) because of potential cardiopulmonary side effects associated with deeper levels of sedation and because there is no reversal agent available (Singh et al., 2008). In the last 15 years clinical use of propofol has expanded to include procedural sedation for endoscopic procedures (Cohen et al., 2007; Ginzburg, Greenwald, & Cohen, 2007; Heuss & Inauen, 2004; Molina-Infante et al., 2012; Singh et al., 2008). While many endoscopists use benzodiazepines and opioids as their conventional sedation regime, the use of propofol, either alone or with fentanyl for analgesia, is increasing as it may have two major advantages: a shorter mean time to sedation and a shorter mean time to full recovery and thereby discharge home (Byrne, Chiba, Singh, & Sadowski, 2008; Külling, Orlandi, & Inauen, 2007; McQuaid & Laine, 2008; Schreiber, 2007; Sipe, Scheidler, Baluyut, & Wright, 2007; Ulmer et al., 2003). Multiple studies have evaluated the use of propofol for procedural sedation and as a result of clinical reports it is now being advocated by a number of professional societies including the Canadian Association of Gastroenterology (CAG), the American College of Gastroenterology (ACG), the American Association for the Study of Liver Diseases (AASLD) and the American Gastroenterological Association (AGA) (Byrne et al., 2008; Porostocky et al., 2011).

Because of increased use of colonoscopy for screening in the general population, recent efforts have focused on developing methods to assist with the safe and efficient administration of sedation and analgesia during endoscopic procedures. A computer-assisted personalized system, Sedasys® System (Ethicon Endo-Surgery, Inc.), has been designed to regulate the delivery of sedation to patients undergoing gastroenterological procedures, particularly in the ambulatory setting. The Sedasys® System uses an automated dosing algorithm designed to titrate propofol sedation slowly in response to the patient's physiologic status (Pambianco, Vargo, Pruitt, Hadi, & Martin, 2011; Sneyd & Rigby-Jones, 2010). The apparatus monitors electrocardiography (ECG), oxygen saturation (Sa02) and exhaled carbon dioxide (C02) in alignment with the recommendations of the American Society of Anaesthesiologist's (ASA) 'Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists' and the Canadian Anesthesiologists' Society (American Society for Anesthesia Task Force, 2002; Merchant, 2013; Sneyd et al., 2010). The device is equipped with safety features including monitoring for over-sedation which is measured by continuous biophysiologic, tactile and auditory assessment of the patient's cardio-respiratory status and reduction or prevention of propofol delivery if oxygen is not being delivered to the patient. The system triggers oxygen to be increased during the propofol infusion in response to hypoxemia and apnea, and the propofol infusion is reduced or stopped at the first sign of over-sedation. When patients, who will receive propofol via the Sedasys® System, are admitted to the endoscopy suite, they are provided with headphones and a hand-held device that has a vibrate function. During the procedure, ongoing assessment of the patient's responsiveness to auditory and tactile stimulation is evaluated by the Sedasys® System as audible commands to grip the vibrating device are delivered through the headphones. In 2010

Health Canada approved the device for use during routine colonoscopy (Banerjee et al., 2011). It was recently adopted for trial to support the safe administration of propofol in a large surgical outpatient unit in an urban health authority in Canada.

1.1 Significance

Procedural sedation used during colonoscopy can enhance patient comfort allowing for complete visualization of the colon, however colonoscopy can be resource intensive because the patient's recovery can be lengthy and may be unpredictable. As demand for colonoscopy services increases there is a need to improve practice efficiencies in the delivery of endoscopy services (Zamir & Rex, 2002). Vargo et al. (2000) suggests cost-efficiency will only be realized if sedation-related issues are addressed through a more rapid discharge or shorter recovery period.

1.2 Statement of Purpose

Several physiological factors can affect patient outcomes when they receive sedation for endoscopic procedures. Sedation and analgesia agents have the potential to delay recovery time and increase the risk of cardiopulmonary complications (Cohen et al, 2007).

The purpose of this study was to examine differences in recovery time and adverse events for patients who received either propofol via the Sedasys® System or midazolam via routine injection during colonoscopy performed by one gastroenterologist in a large surgical outpatient unit in an urban health authority in Canada.

The primary objectives were:

a) To examine differences in procedure length, recovery time and sedation-related cardiopulmonary events between patients who had midazolam versus propofol during colonoscopy.
b) To describe the differences in recovery time and sedation-related cardiopulmonary events by sedation type, sex, age, body mass index (BMI), medication history, medical history and procedure length, between patients who receive midazolam versus propofol during colonoscopy.

Chapter 2: Literature Review

This chapter provides a review of the published literature associated with colonoscopy and three components of endoscopic practice: procedural sedation methods, patient safety elements and throughput efficiencies related to recovery time.

The first section defines the colonoscopy procedure itself and current capacity based on demand for service, and the second compares the benefits and associated risks of two sedation regimens used during the procedure. The remaining sections describe administration techniques, monitoring recommendations and patient characteristics that have the potential to influence patient outcomes, recovery time and subsequent throughput efficiency.

2.1 Search Strategy

A systematic search of the literature was performed using the following bibliographic databases: Medline (EBSCO) from 1989 – July, 2012, EMBASE from 1974 – July, 2012 and Cochrane Database of Systematic Reviews from 2007 – July, 2012. The search terms included the following: “colonoscopy”, “endoscopy”, “colorectal screening”, “midazolam”, “propofol”, “fentanyl”, “conscious sedation”, “safety”, “recovery time”, “complications”, “adverse events”, “age”, “sex”, “body mass index”, “BMI”, and “comorbidity”. Searches were limited to articles published in English and involving human subjects. Additional relevant articles were selected from references within the initial search.

2.2 Colonoscopy and Screening

A colonoscope is a long flexible tube with a camera and a light source at the tip. During colonoscopy the scope is inserted into a patient’s anus and advanced slowly under visual control into the rectum and through the colon to the cecum allowing the endoscopist to

examine the lining of the entire colon and same-time biopsy sampling or removal of pre-cancerous polyps and some early stage cancers (Levin et al., 2008).

The goal of colorectal cancer screening is to detect colorectal cancer early and to prevent the recurrence of benign and malignant tumors thereby reducing the incidence of advanced disease and the rates of morbidity and mortality (Bowles et al., 2004; Colorectal Cancer Association of Canada (CCAC), 2012; CPAC, 2010; Levin et al., 2008; Marrett, De, Aira, & Dryer, 2008; Ries et al., 2008). Early detection saves lives. If colorectal cancer is found before symptoms occur, the cure rate is almost 90% (Barclay, 2012). Despite screening awareness campaigns and the benefits of early detection, a Canadian survey completed in 2009 revealed only 44% of Canadians between the ages of 50 and 74 are participating in screening programs recommended by the Canadian Cancer Society (CPAC, 2010). The Canadian Association of Gastroenterolgy and the Canadian Digestive Health Foundation recommend individuals with average risk who are between the age of 50 and 65 years should have a screening colonoscopy every ten years (Leddin et al., 2010).

2.3 Procedural Sedation

Procedural sedation is a technique of administering sedative agents with or without analgesics resulting in a depressed level of consciousness where the patient is able to tolerate unpleasant procedures while still able to independently maintain cardiorespiratory function and the ability to respond purposefully to verbal or tactile stimuli (Leslie & Stonell, 2005; Sheta, 2010; Standards of Practice Committee, 2008). Sedation is intended to reduce the patient's anxiety and discomfort, improve their tolerance for the procedure, minimize their risk of physical injury and provide the endoscopist with an ideal environment for a thorough examination (Cohen et al., 2010; Lubarsky, Candiotti, & Harris, 2007; Molina-Infante et al.,

2012; Park et al., 2007; Schreiber, 2007; Standards of Practice Committee, 2008). In a 2006 retrospective analysis of 236,087 outpatient colonoscopies performed in Germany, researchers concluded that the administration of sedation/analgesia reduced the risk of incomplete examination by half resulting in a higher rate of adenoma detection (OR 0.51, 95% CI: 0.41-0.63) (Crispin, Birkner, Munte, Nusko, & Mansmann, 2009). An observational study involving 673 endoscopists who performed colonoscopies across 278 practice sites compared patients who received three types of sedation to those who did not receive sedation: a benzodiazepine alone, a benzodiazepine with an opioid, or a benzodiazepine with propofol (Radaelli et al., 2008). Researchers reported the use of sedation overall (n = 12,835) resulted in a significant increase in the incidence of successful colonoscopy completion when benzodiazepines were used in combination with an opioid (OR 2.1, 95% CI: 1.8-2.6) or propofol (OR 2.3, 95% CI: 1.6-3.5) (Radaelli et al., 2008). Moreover, the use of the combination of sedatives and analgesics (compared to sedatives alone) was significantly associated with polyp detection and removal (OR 1.172, 95% CI: 1.074-1.286) (Radaelli et al., 2008).

2.4 Medications Used for Procedural Sedation

Ideal agents for endoscopic procedures have a rapid onset, a short duration of action, maintain hemodynamic stability and do not incur side effects (Wiggins, Khan, & Winstead, 2010).

2.4.1 Benzodiazepines

Among the most commonly used benzodiazepines, midazolam is favoured because of its faster onset, shorter duration of action, high amnesic effect and the availability of pharmacological antagonists (reversal agents), such as flumazenil, to counteract the effects of

oversedation (Cohen, Hightower, Wood, Miller & Aisenberg, 2004; Waring et al., 2003). Midazolam has a half-life of 30 minutes. Benzodiazepine-related adverse events are associated with rapid administration resulting in deeper sedation, an increased risk for oxygen desaturation, cardiorespiratory complications and a prolonged recovery period; when combined with an opioid these effects are intensified (Olkkola & Ahonen, 2008; Rex, 2006; Ulmer et al., 2003; Wiggins et al., 2010). Moreover, midazolam is lipophilic and can be sequestered in adipose tissue resulting in an unpredictable time from administration to peak effect ranging from 30 to 60 minutes, therefore patients who are obese, older or those with hepatic or renal impairment are at risk for prolonged sedative effects because of delayed drug clearance (Cohen et al., 2010; Wiggins et al., 2010).

2.4.2 Fentanyl

Colonoscopy is most often performed with a combination of an opioid and a sedative agent as its synergistic effect improves colonoscopy completion rates and increases patient satisfaction (Rex, Overley, & Walker, 2003). Fentanyl is one of the most commonly used opioids for this purpose because of its fast onset of action (1-2 minutes) and rapid clearance (30–60 minutes), and because it results in less nausea than other opioids (Cohen et al., 2007; Triamtafillidis et al., 2013; Wang et al., 2011). Fentanyl produces a generalized central nervous system depression by altering pain reception and inhibiting pain pathways and must be used cautiously, particularly with individuals who consume other CNS depressants such as other opioids, sedatives, phenothiazines, tranquilizers and antihistamines (Huang et al., 2004; Rex, 2006; Waring et al., 2003). In high doses fentanyl can cause muscular rigidity in the chest wall and may result in respiratory insufficiency (Rex, 2006; Waring et al., 2003).

2.4.3 Propofol

Propofol is a short acting hypnotic agent with a plasma half-life of 1.3 – 4.1 minutes (compared to 30 minutes for midazolam), and a time to peak effect of 60–100 seconds which results in a rapid decline of propofol concentrations permitting rapid awakening even after prolonged administration (Byrne et al., 2008; Chutkan et al., 2004; Heuss et al., 2004; Standards of Practice Committee, 2008). Propofol has minimal analgesic properties and is therefore often used in combination with an analgesic, however dosage is often reduced when combined with an opioid such as fentanyl (Heuss et al., 2004; Voynarovska & Cohen, 2008). Propofol's action is almost instantaneous and the patient may slip rapidly and unintentionally into a level of deep sedation, potentially impairing spontaneous ventilation and cardiovascular stability (Byrne et al., 2008; Cohen et al., 2003; Heuss et al., 2004; Pambianco, Whitten, Moerman, Stuys, and Martin, 2008; Sieg, 2007). Clinical use of propofol has expanded to include lighter levels of sedation used for endoscopic procedures (Cohen et al., 2007; Heuss et al., 2004; Molina-Infante et al., 2012). In contrast to benzodiazepines, there is no specific antidote for propofol therefore patients who are over-sedated may require resuscitation (Heuss et al., 2004; Lee, C. et al., 2011; Rex, Deenadayalu, & Eid, 2008; Tohda et al., 2006).

2.5 Patient Risk Related to Endoscopic Procedures

Despite the benefits, use of sedatives and/or analgesics remains risky during endoscopy; procedural sedation is associated with oversedation that leads to arterial desaturation and hypoxemia (American Society of Anesthesiologists Task Force, 2002, p. 1008; Cohen et al., 2007; Corlin & Bedford, 2011; Maurer & Philip, 2010; Ristikankare et al., 2000; Rozario, Sloper, & Sheridan, 2000). Excessive sedation may induce respiratory

depression and prolonged recovery, particularly in older adults (OR 1.02, CI: 1.01-1.02, p<0.001) and in those with comorbid cardiorespiratory disease (OR 1.5, CI: 1.3-1.7, p <.001) (Sharma et al., 2007).

Although colonoscopy is rarely associated with potentially life-threatening complications including cardiorespiratory compromise, adverse event reports are associated more frequently with colon perforation and bleeding rather than cardiorespiratory complications (Crispin et al., 2009; Singh et al., 2009; Vargo, 2007). In Canada, actual numbers of colonoscopy-related adverse events are not available since electronic reports are rarely available outside of tertiary care centers and reporting is primarily being done on paper-based forms (Singh et al., 2009). The American Society of Anesthesiology (ASA) has defined four levels of sedation: minimal, moderate, deep sedation and general anesthesia with moderate being the target sedation level for endoscopic procedures (Cohen et al., 2004). The 2008 hospital accreditation standards defined by The Joint Commission and the Canadian Anesthesia Society recommends qualified individuals who administer sedation must have education, training and experience evaluating patients' pre-sedation state, in rescuing patients who progress into a deeper level of sedation and in managing cardiopulmonary complications (The Joint Commission, 2013; Merchant, 2013).

2.6 Risk Related to Propofol Compared to Benzodiazepines

There has been emerging consensus over the last decade that propofol administered by endoscopists in appropriately selected patients is effective and has safety standards comparable to traditional sedation (Byrne et al., 2008; Cohen, 2011; Schreiber, 2007; Wehrmann & Triantafyllou, 2010). One researcher detected no significant difference in the incidence of hypoxemia: RR 1.11, 95% CI: 0.71-1.74 (McQuaid et al., 2008). Moreover, a

systematic review of five studies (n=407) reported no significant difference in the number of patients developing hypoxia when comparing propofol alone to traditional sedation (benzodiazepines including diazepam or midazolam and opioids including pethidine, fentanyl, remifentanil or alfentanil), OR 0.69, 95% CI: 0.25-1.89 (Singh et al., 2008). A recent meta-analysis of 12 randomized controlled trials (n=1,162) comparing propofol for colonoscopy (n=634) to midazolam (n=527) reported lower risk for hypoxemia and hypotension (OR 0.4, 95% CI: 0.2-0.79) (Quadeer, Vargo, Khandwala, Lopez, & Zuccaro, 2005). A systematic review reported a significant reduction in recovery time (minutes) when comparing propofol alone to traditional sedation (described above), n=249 (-14.68 95% CI: -19.79 to -9.58) (Singh et al., 2008). Moreover, one study reported an eleven minute reduction in recovery time when propofol was used (mean recovery time 16.5, SD 8.5 minutes) versus midazolam ((mean recovery time 27.5, SD 16.2 minutes); $p = 0.0001$) (Ulmer et al., 2003).

2.7 ASA Classification

Endoscopists use a risk classification system to screen colonoscopy patients for risk of cardiovascular and respiratory problems during procedures. The tool, based on the classification of the American Society for Anesthesiology (ASA) is completed by the physician during the pre-procedure history and physical examination (See Appendix A) (ASA, 2002; Armstrong et al., 2012; Gašparović, Rustemović, Opačić, Bates, & Petrovecki, 2003; Quadeer, Lopez, Dumot, and Vargo, 2009; Rex et al., 2002; Schreiber, 2007; Ulmer et al., 2003).

In their guideline for gastrointestinal endoscopy procedural sedation, Riphaus et al. (2009) state patients with advancing age and concomitant conditions, particularly coronary or

pulmonary disease, rank higher in ASA classification and those with ASA classification III or higher are at greater risk for complications during procedural sedation. In the US a cohort study was conducted between 1998 and 2003 across 69 practice sites with 593 endoscopists and 11,683 colonoscopies (Vargo, Holub, Faigel, Lieberman, & Eisen, 2006). Researchers estimated the adjusted relative risk (ARR) for cardiopulmonary events while controlling for confounders and reported ascending ASA physiologic classification was associated with a greater risk for cardiopulmonary events: ASA I - II = Adjusted Relative Risk (ARR) 1.0; ASA III – V = Adjusted Relative Risk (ARR)1.96, 95% CI: 1.36-2.83. Sedation administered by endoscopists without anesthesia support is generally considered appropriate for ASA I – III patients (Riphaus et al., 2009; Schreiber, 2007; Ulmer et al., 2003; Vargo et al., 2006; Wiggins et al., 2010).

2.8 Measuring Levels of Sedation

The administration of sedation and analgesia results in a continuum of progressive impairment in consciousness and depending on what is used to achieve the goal of sedation, patient comfort or anesthesia, varying depths of sedation may be achieved including: minimal (anxiolysis), moderate (conscious sedation), deep, and general anesthesia (Cohen et al., 2007; Heuss et al., 2004; Ulmer et al., 2003; Vargo, Cohen, Rex, & Kwo, 2009). Sedative and analgesic agents induce responses that progressively transition sedation depth and the continuum of states of consciousness are difficult to control, therefore a validated scale, the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S), is widely used as a standard in clinical practice to reduce the risk of over-sedation (American Association of Anesthesiologists, 2002; Riphaus et al., 2009, Shah & Cohen, 2010). The observer rates patient responsiveness, speech and facial expression/eye movements to classify a real time

stimulus-response relationship to guide titration of sedation and analgesia and reduce the risk of over-sedation (Shah et al., 2010).

A systematic review and meta-analysis of sedation used for adult patients having routine endoscopy procedures (n = 3,918) reported a moderate depth of sedation has the lowest risk for sedation-related adverse events (McQuaid et al., 2008). Two of the studies comparing midazolam and an opioid (meperidine or fentanyl) for colonoscopy reported no significant difference in the incidence of bradycardia (OR 1.00, 95% CI: 0.30-3.36), hypotension (OR 1.28, 95% CI: 0.51-3.26) or hypoxemia (OR 0.82, 95% CI: 0.22-2.98). Moderate sedation is considered the optimum depth for most endoscopic procedures including colonoscopy as it provides the best balance between safety and effectiveness; an amnesic effect and adequate patient comfort while allowing for spontaneous cardiorespiratory function and the ability to communicate with clinicians (Cohen, 2008b; Cohen et al., 2010; Leslie et al., 2005). At this level of sedation, ventilatory and cardiovascular function is maintained and the patient is able to respond purposefully to verbal or mild tactile stimulation (Odom-Forren, 2008; Waring et al., 2003).

Table 2.1 Definitions of General Anesthesia and Levels of Sedation/Analgesia

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Procedural or Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsive-ness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be in adequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

In reality, despite the intent to target a moderate level, wide variations in sedation depth exist because of the practice differences between practitioners, training for sedation administration, and differences in patient characteristics such as age, health status, concurrent medications, pre-procedure anxiety, and pain tolerance (Leslie et al., 2005; Standards of Practice Committee, 2008; Vargo et al., 2000). Moreover, sedation level may change during the procedure as the level of stimulation changes. A patient who is moderately sedated as the colonoscope is advanced through the colon may become deeply sedated as it is withdrawn because painful stimulation is significantly reduced (Voynarovska et al., 2008). As depth of sedation progresses from moderate to deep, so does the risk for cardiopulmonary complications (Cohen, 2008b; Rex, 2006). At the level of deep sedation patient responsiveness is usually limited to purposeful responses to painful stimuli, however these patients are at risk for developing airway obstruction and loss of respiratory drive airway support may be required. At the level of general anesthesia, the patient is unarousable, even to painful stimuli (Waring et al., 2003).

2.9 Titration of Sedation

Benzodiazepines alone or in combination with an opioid for colonoscopy is traditionally administered manually by the endoscopist. Depending on the pharmacodynamic property of the opioid selected and the volume administered, sedation depth sometimes increases unintentionally putting patients at risk for respiratory depression, myocardial depression and arrhythmias (Sheta, 2010). Drug dosing should always be titrated in small doses over several minutes to a desired clinical and physiological effect (Olkkola et al., 2008; Sneyd et al., 2010). The concentration-effect relationship may differ significantly from one person to another, particularly in the obese and elderly individuals as well as those with

chronic lung disease (Cohen, 2008b; Lugay, Otto, Kong, Mason, & Wilets, 1996; Triantafillidis et al., 2013; Rex, 2006). ASA clinical guidelines call for the cautious titration of sedative medications using small incremental doses and allowing sufficient time between doses to observe the effect (ASA, 2002; Morrow et al., 2000). Others suggest that sedation doses should be reduced and the intensity of intra-procedural monitoring should be increased in patients with higher risk for surgical complications (Rex et al., 2002).

During colonoscopy an initial dose of a sedative and an analgesic agent is administered using clinical estimation (based on age, height and weight). Subsequent doses are administered after the initial dose in an attempt to achieve a level of moderate sedation. Patients can easily become over-sedated because the peak effect for benzodiazepines and opioids can range from 30 to 60 minutes and if the procedure lasts 20 to 30 minutes, the peak effect of the drugs delivered can occur in the recovery phase following the procedure (Huang et al., 2004).

2.10 Monitoring Recommendations

Patient monitoring during procedural sedation is vital and should not only involve quantitative physiological measurements (pulse rate, oxygen saturation and blood pressure), but also qualitative visual observation of respiratory rate and effort and level of consciousness (Konairis, Wilson, Drugas, & Simmons, 2003). Alterations from baseline may reveal early signs of impending cardiovascular dysfunction such as reduced blood pressure or oxygen desaturation or arrhythmias (Doyle, 2009; Ginzeberg et al., 2007; Godwin et al., 2005; Standards of Practice Committee, 2005).

Standard monitoring during the procedure and recovery period should include the measurement of pulse rate, oxygen saturation and blood pressure and when propofol is used

the Canadian Association of Gastroenterology (CAG) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend the use of continuous electrocardiography (Dumonceau et al., 2010; Porostocky et al., 2011; Wiggins et al., 2010). During routine procedures in low risk ASA I or II patients using traditional sedation, the role of continuous ECG monitoring has not been established, however it is recommended per ASA guidelines for patients with a history of cardiovascular disease and dysrhythmias, pulmonary disorders, the older adults or when lengthy procedures are anticipated (Cohen et al., 2007; Wiggins et al., 2010). Pulse oximetry provides continuous measurement of arterial oxygen saturation and is a reliable method for detecting decreases in oxygen saturation and heart rate changes, although it is not able to detect early decreases in the adequacy of ventilation or the onset of hypercarbia that precedes the development of apnea (Godwin et al., 2005). End tidal CO2 monitoring (capnography) is a noninvasive method for measuring real-time respiratory activity and changes allows for detection of hypoventilation or apnea earlier than either visual observation, skin colouration or pulse oximetry (Cirgin Ellet, 2010; Cohen et al., 2007; Waring, 2003). Others argue that though this technique shows promise, there is no evidence to support that is has improved patient outcomes and there is insufficient data to support a recommendation for routine use of capnography (Cohen et al., 2007; Doyle, 2009; Faigel et al., 2002; Godwin et al., 2005; Riphaus et al., 2009; Wiggins et al., 2010). A delay in the recognition of hypoventilation is very often well tolerated by patients, although it may be problematic in prolonged procedures or in high-risk patients (Ginzburg et al., 2007; Koniaris et al., 2003).

2.11 Procedural Sedation and Patient Characteristics

Individual patient characteristics (sex, patient age, a history of pelvic or abdominal surgery and drug metabolism) have the potential to influence drug metabolism, endoscopy completion, and subsequently procedure and recovery time. A presence of comorbidities such as cardiovascular, pulmonary, renal, hepatic disease and morbid obesity increase the risk for cardiovascular complications during endoscopy with procedural sedation (Mauer et al., 2010; Waring et al., 2003).

Sex-related pharmacokinetic differences include: physiology, body weight, organ size, glomerular filtration rate, and differences in gastric motility (Freire et al., 2011; Meibohm, Beierle & Derendorf, 2002). In general men have more musculature that prevents the colonoscope from looping during the endoscopy (Saunders et al., 1996). However, women have less musculature and a greater colonic length than men (108 – 206 cm versus 97-205 cm), $p = 0.005$, predisposing women to colonic loop formation resulting in a more difficult, lengthened endoscopic procedure (Anderson et al., 2001; Ristikankare, Hartikainen, Heikkinen, Janatuinen, & Julkunen, 2001; Saunders et al., 1996). Greater visceral fat disposition, intra-pelvic volume differences and previous pelvic surgery may also contribute to more difficult cecal intubation rates for women (Ristikankare et al., 2001). However, the relationship between pelvic surgery and procedural length are inconsistent; Ristikankare (2001) reported longer procedure time for women who had previous pelvic surgery (34.2 minutes (SD = 14.7) versus 27.5 minutes (SD = 12.2), $p < 0.05$); however another study reported pelvic surgery was not significantly related to difficult colonoscopy and longer procedure time (OR 1.05, 95% CI: 0.55-2.00, $p = 0.89$) (Anderson et al., 2001). Women also tend to have lower glomerular filtration rates (approximately 10% lower) and slower gastric

motility than men, resulting in a reduced filtration and excretion of sedative and analgesic medications potentially predisposing them to prolonged recovery and cardiopulmonary risk associated with over-sedation (Meibohm et al., 2002). Body fat composition may also affect drug distribution, particularly for lipophilic drugs such as benzodiazepines and opioids, therefore distribution volume will generally be higher in females than in males (Pleym, Spigset, Karachi, & Dale, 2003).

Aging is associated with a decline in organ function and it must be recognized that it is not age, but co-existing age-related co-morbid conditions combined with excessive or rapid dosing of sedative agents that contributes more significantly to cardiopulmonary complications (Eisen et al., 2000; Kanonidou et al., 2007; Waring et al., 2003). Researchers have employed various data collection approaches when measuring age in relation to the incidence of sedation-related cardiopulmonary events. Several studies measured physiological factors associated with age-related decline in functional status (co-morbid conditions), however most have simply measured actual age (in years). Sharma et al.'s (2007) five year review measured age (≤ 60 years and > 60 years) and ASA classification (the existence of co-morbid conditions) and analyzed these parameters separately to examine their relationship with sedation/analgesia related cardiopulmonary events. This extensive national health record review of 335,249 endoscopic procedures performed by 593 endoscopists across 81 endoscopy sites across the United States reported older age was a significant independent predictor for cardiopulmonary unplanned events (OR 1.02, 95% CI: 1.01-1.02, p <.001*)* (Sharma et al., 2007). Moreover, existing comorbid conditions were also a significant predictor of the cardiopulmonary unplanned events (ASA I or ASA II: 1.05,

95% CI: 0.95-1.16; ASA III: 1.8, 95% CI: 1.6 -2.0; ASA IV: 3.2, 95% CI: 1.3-1.7 (Sharma et al., 2007)

Advancing age is also associated with a reduction in body fat stores and lipid soluble drugs such as benzodiazepines may have a prolonged half-life, delaying recovery for this group (Eisen et al., 2000; Quadeer et al., 2009; Triantafillidis et al., 2013). Altered pharmacologic drug distribution combined with age-related reduced hepatic and renal clearance mechanisms, can also prolong recovery following sedation and increase the risk for sedation-related adverse events for older adults. Moreover, centrally acting substances including opioids produce greater respiratory depression and a greater incidence of transient apnea (Qureshi et al., 2006; Riphaus et al., 2009). It is therefore recommended that older patients receive substantially lower initial doses of all sedation/analgesia agents with a short half-life, be administered at a reduced rate, followed by slower gradual doses titrated to patient response (Cohen et al., 2007; Huess et al., 2004; Qureshi et al., 2006; Riphaus et al., 2009; Triantafillidis et al., 2013).

A study conducted in the US in 2009 (n = 79) explored possible predictors of hypoxemia for patients who receive a benzodiazepine and an opioid during an endoscopic procedure. Researchers reported hypoxemia occurred more frequently in patients who were ≥ 60 years of age ($p = 0.032$) (Quadeer et al., 2009). A systematic review conducted in 2011 explored computerized bibliography data bases to examine the association between age and the incidence of cardiovascular /pulmonary events among elderly patients who had sedation for colonoscopy (Day, Kwon, Inadomi, Walter, & Somsouk, 2011). Researchers reported the incidence of sedation-related adverse events was 6.3 / 1000 patients (95% CI: 5.7-7.0) for patients who were ≥ 66 years of age.

According to the World Health Organization (2013), Body Mass Index (BMI) is a simple method of combining weight and height and is commonly used to classify underweight, normal weight, overweight and obesity in adults. Patients who are morbidly obese may be at increased risk for sedation-related complications including pulmonary hypertension, obstructive sleep apnea, and restrictive lung disease (Huang et al., 2004; Triantafillidis et al., 2013; Waring et al., 2003). One study (n = 79) examined the relationship between obese (BMI ≥ 30) and normal weight (BMI < 30) patients and the incidence of hypoxemia during procedural sedation. Researchers reported although BMI correlated with the number of hypoxemic events, the effect for BMI to predict hypoxemia was not statistically significant: with every 5U (5 kg/m^2) increase in BMI, the risk for hypoxemia increased by 1.6 (OR 1.6, 95% CI: 0.95-2.60, $p = 0.079$ (Quadeer et al., 2009).

Other factors that may influence a patient's response to procedural sedation include concurrent use of central nervous system (CNS) depressing medications such as sedatives or anxiolytic medications, tranquilizers, phenothiazines, antihistamines, or other opioid agents (Huang et al., 2004; Standards of Practice Committee, 2008; Waring et al., 2003).

2.12 Processes Related to Colonoscopy

Utilization of colonoscopy procedures continues to rise and the overall procedure and recovery time are resource intensive, therefore improving efficiencies in the delivery of endoscopy is an important potential mechanism to meet the rising demand for endoscopic services.

2.12.1 Procedure and Recovery Time Associated with Sedation and Analgesia

Procedure time typically refers to the length of time between start and end of the endoscopy procedure. A systematic review of published articles and abstracts reported that

procedural sedation using propofol versus midazolam for colonoscopy did not result in a significant difference in procedure times (Vargo et al., 2009). Further, Ulmer (2003) compared procedure times for patients undergoing outpatient colonoscopy (n = 100) by measuring time of scope insertion to time the cecum was visualized and reported the procedure time was shorter for the propofol group, however this was not significant (propofol = 3.15 ± 1.67 minutes versus midazolam = 3.75 ± 1.76 minutes, $p = 0.08$).

Recovery time (the time between end of procedure and patient discharge) is important to evaluate to manage throughput efficiencies. Traditionally, sedation and analgesia are administered intravenously using a syringe. A randomized blinded study involving 80 outpatients who received manual administration with an intravenous bolus of either propofol alone or midazolam and meperidine during colonoscopy reported mean time (arrival in recovery area to discharge) to be significantly shorter for those who received propofol (14.4 minutes (SD = 6.5)) that for those who received midazolam and meperidine (33.0 minutes (SD = 23.3)) (Sipe et al., 2002). In a randomized blinded study involving 100 outpatients, researchers reported patients who received manual intravenous administration of a propofol bolus for colonoscopy required significantly less time to reach full recovery (16.5 minutes) than those who received midazolam (27.5 minutes) $p = 0.0001$ (Ulmer et al., 2003).

A randomized, non-blinded study examined recovery time and the incidence of sedation-related adverse events by comparing propofol administered using a computer assisted personalized delivery system (Sedasys® System) (n = 489) and standard sedation, (manual administration of a benzodiazepine and an opioid) (n = 493) (Pambianco et al., 2011). Patients receiving propofol recovered significantly faster than those receiving standard sedation ($p > .001$).

2.12.2 Sedasys® System

Propofol is generally associated with good hemodynamic stability, however it can induce bradycardia and transient decreases in blood pressure, particularly with bolus administration (Triantafillidis et al., 2013). Several propofol infusion platforms have been created to address the inherent safety risk associated with the administration of propofol (Sneyd et al., 2010). The Sedasys® System consists of two major components: a drug delivery system and a patient monitoring system. This device uses proprietary software and is a "closed-loop" system that incorporates feedback from a real-time measure of drug effect designed to target and maintain minimal-moderate sedation (Cohen & Benson, 2009; Pambianco et al., 2011; Sneyd et al., 2010). It is purported to safely administer propofol through precise control of the depth of sedation (Leslie, Absalom, & Kenny, 2002; O'Connor, Morain, & Vargo, 2010; Pambianco et al., 2008; Pambianco et al., 2011; Van der Linden, 2010). This device monitors the patient's physiological status based on accepted monitoring recommendations included in the American Society of Anesthesiologists (ASA) 'Practice Guidelines for Sedation and Analgesia by Nonanesthesiologists' (ASA. 2002). While multiple physiologic feedback parameters are continually recorded, pulse oximetry, blood pressure, electrocardiography, end-tidal carbon dioxide, and automatic response to otic (via an earpiece) and tactile stimuli (via a vibrating hand held piece), propofol infusion is slowly titrated to maintain a desired plasma concentration level based on a computerized drug delivery algorithm (Pambianco et al., 2008; Riphaus et al., 2009; Standards of Practice Committee, 2008; Wiggins et al., 2010). The device prevents administration of propofol unless oxygen is being delivered to the patient. Indicators of oversedation such as oxygen desaturation, a low respiratory rate and apnea trigger a system response; the patient will be

stimulated to respond, oxygen flow will be increased, and the propofol infusion may be reduced or stopped (Cohen et al., 2009; Banerjee et al., 2011; Pambianco et al., 2011; Vargo, 2004). The US Food and Drug Administration (FDA) and Health Canada has approved the Sedasys® System for use during routine colonoscopy (U.S. Food and Drug Administration, 2013; Sneyd et al., 2010).

2.13 Conclusion

Benzodiazepine and opioid combinations are still the most widely used sedative/analgesic agents for procedural sedation, and although they provide acceptable sedation and analgesia they are associated with undesirable side effects and residual effects and they fall short of the pharmacokinetic profile suggested for optimal procedural sedation and analgesia. Although the use of propofol has been investigated intensively as a form of procedural sedation, it has been evaluated with manual administration of an intravenous bolus and to-date, limited research has examined recovery times when comparing propofol administered with a computerized delivery to benzodiazepines administered manually with an intravenous bolus.

The studies included in this review of the literature examined various combinations of sedation and analgesia options used during colonoscopy. Researchers also used inconsistent groupings and means of measuring predictor variables to calculate differences in patient outcomes, procedure and recovery times. Upon examination of the current available literature, it is apparent data on the outcomes and side effects of sedation in older patients are limited and there is a notable lack of consistency in measuring outcomes when exploring age and its association with sedation-related cardiopulmonary events. Moreover, there is a lack of research that has explored the relationship between body weight and the risk for sedation-

related adverse events. While Ginzburg, Greenwald, and Cohen (2007) state "a patient with significant cardiac history is more likely to suffer an adverse event from sedation" and "a patient's pre-procedure medical condition may affect his or her ability to tolerate a subsequent complication" (p. 405), limited research has examined the relationship between ASA classification (medical history) and recovery time for colonoscopy. There was also a lack of research associated with medications taken and the effect on recovery time and sedation-related cardiovascular risk.

This chapter has described a variety of sedative/analgesic and administration options for colonoscopy, the implications for cardiopulmonary risk and the impact on recovery time. The next chapter will outline the research design, method and procedures used to evaluate the differences in patient outcomes for patients receiving midazolam or propofol in this surgical outpatient unit.

Chapter 3: Methods

This retrospective chart review compared 100 consecutive records where the patient received a manual intravenous dose of midazolam and fentanyl and a second group of 100 records where the patient received intravenous fentanyl and a computer-assisted personalized intravenous dose of propofol using the Sedasys® System. The midazolam group was used as the comparison group. Information was extracted from an ongoing quality improvement project that is associated with the Sedasys® System used in a surgical outpatient unit. The researcher, who is also leading the quality improvement project in this unit, collected the data.

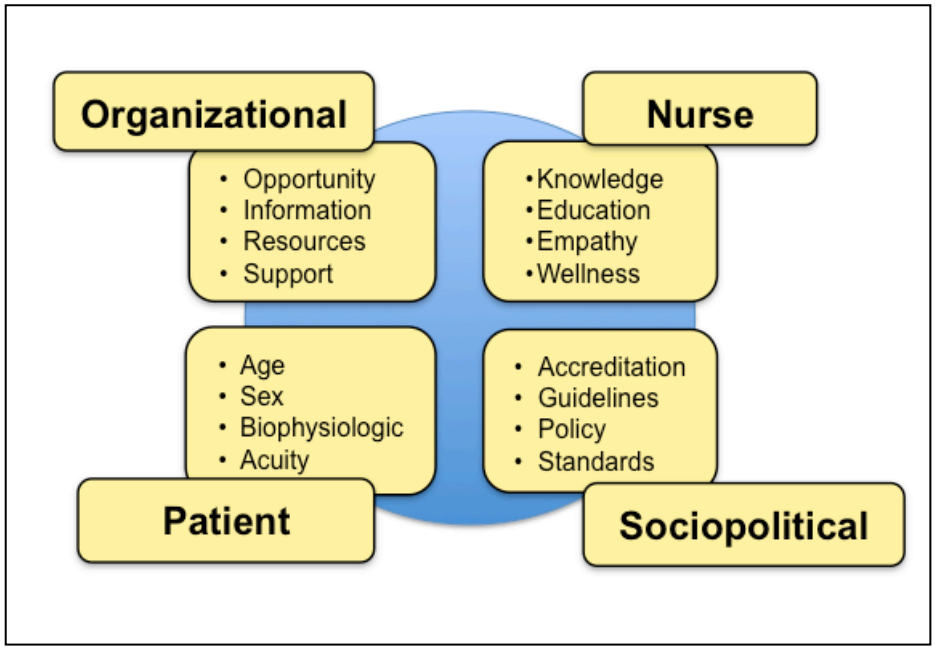
This chapter presents the theoretical model used to guide the study and describes the study methods including the research question and hypothesis, operational definitions, setting and sample selection procedure, ethical considerations, data collection process, and statistical analysis. Assumptions and issues of rigor are also included in this chapter.

3.1 Theoretical Framework: Theory of Knowledge Use in Pain Care (KUPC)

Knowledge utilization is an essential component of nursing practice and our current healthcare system. Latimer, Ritchie and Johnston (2010) identified a gap between research evidence and knowledge use and developed a conceptual model to explain knowledge translation in pain care and to stimulate the use of research in practice. This research was guided by a conceptual framework; Knowledge Use in Pain Care (KUPC) (Latimer, Ritchie, & Johnston, 2010). Latimer et al. suggest that two processes influence knowledge utilization: the acquisition of relevant knowledge and the context that facilitates its application. The model consists of four main components that collectively contribute to the provision of evidence-based patient care: organizational factors, individual nurse characteristics, patient

characteristics, and external sociopolitical factors that may impact the nurse's ability to make clinical decisions that lead to quality and best patient outcomes (Baker, Ellett, & Sharon, 2010; Latimer et al., 2010). (see figure 3.1)

Figure 3.1 Knowledge Use in Pain Care (KUPC) (Latimer et al., 2010)



Within this model, the organizational variables are drawn from power and opportunity in Kanter's Structural Theory of Organization Behaviour (1993) whereby it is believed employees who are given the opportunity to enrich their practice knowledge and skills are motivated to achieve goals and motivate others (Kanter, 1993; Latimer et al., 2010). The KUPC framework emphasizes the value in providing nurses with a variety of educational opportunities such as inservices, courses, workshops, and conferences to improve knowledge and enhance clinical practice. Educational information, readily available expert mentors, and collaborative relationships among physicians and nurses are all considered integral to an effective work environment (Latimer et al., 2010, McKay & Crippen, 2008).

Moreover, access to trained staff, equipment, supplies, and adequate time to perform the work are believed to contribute to improved client care and outcomes (Latimer et al., 2010).

The KUPC theory posits that skill mix and staff expertise have as much of an influence on patient outcomes as staffing levels and that adverse events are reduced when the skill mix includes a greater number of experienced nurses and/or a charge nurse (Latimer et al., 2010; Tibby, Corea-West, Durward, Ferguson, & Murdoch, 2004). Tibby (2004) conducted a prospective observational study in a pediatric intensive care unit, exploring the association of the occurrence of adverse events by organizational versus individual risk factors (n = 816). Researchers reported a significant association between nursing inexperience (OR 0.71, 95% CI: 0.54-0.94, $p = 0.02$) and nursing supervisory issues (OR 1.35, 95% CI: 1.05-1.75, $p = 0.02$) and the incidence of adverse events (Tibby et al., 2004). Moreover, knowledge, nursing experience and work cultures that encourage critical thinking are considered fundamental to professional accountability and better care (Profetto-McGrath, 2003). Nurses who think critically are "more apt to focus on the circumstances surrounding practice related issues, separate relevant information from irrelevant data, make clinical inferences from the data and remain open-minded to interpret and evaluate findings in relation to other evidence," hence the importance of an organization that supports this approach (Profetto-McGrath, 2003. p. 3).

A Canadian study surveyed neonatal intensive care units nurses (n = 93) in two large tertiary care centres (Latimer, Johnston, Ritchie, Clarke, & Gilin, 2009). Researchers explored the nurse's use of evidence-based protocols to manage pain associated with heel lance and intravenous initiation (170 procedures), and reported nurses' knowledge, experience and education were not significant predictors of evidence-based care. The

provision of pain care was more likely to meet evidence-based standards with a more collaborative relationship between physicians and nurses (OR 1.44, 95% CI: 1.05-1.98, p = 0.02), a higher patient acuity (OR 1.21, 95% CI: 1.06-1.39, p = <0.001) and an unexpected increase in work assignment (OR 1.55, 95% CI: 1.04-2.30, p = <0.001) (Latimer et al., 2009). Thus an organizational structure that considers health care provider collaboration, patient acuity and increased staff workloads supports improved levels of pain care.

Patient factors including biophysiological measurement may be influenced by nurse-physician and organizational factors such as clinical education, staffing dynamics, workload, practice guidelines, etc. As well, patient acuity may influence the nurses ability manage workload consistently. External structures including professional associations, national and regional standards, and governing bodies may also influence organizational function and care delivery (Latimer et al., 2010).

Evidence-informed practice plays an important role in promoting positive patient outcomes, however a gap exists between what we know from research and what we use in practice. Latimer's conceptual model describes the interplay between knowledge translation and utilization factors within the context of nursing care, patient characteristics, organizational resources and sociopolitical support (Baker et al., 2010, Latimer, 2010). This multidimensional model was used in this study to explore the outcomes of procedural sedation during colonoscopy including the variables of interest (procedure time, recovery time and the incidence of sedation-related cardiorespiratory events) within individual patient characteristics (age, BMI, medication history and medical history). The methods used to measure each of these variables is described later in this chapter.

Sociopolitical factors associated with this study include national and international guidelines related to the provision of anesthesia and procedural sedation. ASA classification was used to include and exclude participants and the Modified Observer's Assessment of Alertness /Sedation Scale (MOAA/S) was used to assess recovery from procedural sedation and to evaluate readiness for discharge home. These factors are described in more detail later in this chapter.

Organizational and nurse factors were not directly measured in this study, however they are reflected in the description of the setting.

3.2 Study Setting

This study was conducted in a large surgical outpatient endoscopy unit in an urban health authority in Canada. Registered nurses with extensive experience in endoscopy were offered an opportunity to participate in the trial and were provided with endoscopy and procedural sedation standards, practice guidelines, trial guideline, resources and training related to sedation/analgesia pharmacology and recovery. Extensive education and ACLS certification was also provided and are outlined later in this chapter. Collaborative relationships between the nursing team and the physician involved were encouraged and supported throughout the trial. All participants were involved in weekly huddles to discuss trial progress, patient outcomes and supportive mentorship as needed.

3.3 Research Design

A non-experimental descriptive study was undertaken to examine the differences between two procedural sedation and analgesia regimes used during elective colonoscopy. A retrospective design was selected to examine the differences in recovery times for patients who received either standard of care (midazolam) and an opioid (fentanyl) via manual

injection, or propofol and fentanyl via the Sedasys® System. Secondary outcomes included examination to determine if the effects of sedation dose, sex, body mass index (BMI), current medication history, medical history or duration of the procedure influenced recovery time or the incidence of sedation-related cardiopulmonary events. Data were collected between May 25, 2012 and October 5, 2012 from the Meditech® scheduling system, a health information management software program used for both scheduling and scanning and archiving.

3.4 Research Questions

The study was designed to explore the following research questions:

1. Is there a difference in procedure length or recovery time between patients who had midazolam and those who had propofol sedation during colonoscopy?
    1a. Is there a difference in procedure length or recovery time between males and females among those who had midazolam and those who had propofol administered for sedation during colonoscopy?
2. What are the predictors of recovery time for patients who received midazolam or propofol during colonoscopy?
3. Is there a difference in the number of sedation-related cardiopulmonary events among those who had midazolam and those who had propofol administered for sedation during colonoscopy?

3.5 Hypothesis

The study had two non-directional hypotheses:

i) Among patients who have procedural sedation for colonoscopy, there is a difference in recovery time between those who have midazolam and those who have propofol

ii) Among patients who have procedural sedation for colonoscopy, there is a difference in the number of sedation-related cardio-pulmonary events between those who have midazolam and those who have propofol.

3.6 Operational Definitions

Patient-associated operational definitions used to measure outcomes assessment are described. These include intrinsic variable measurement (age, BMI, medication history, medical history, ASA classification) and extrinsic variable measurement (procedure time, recovery time, adverse cardiopulmonary events).

3.6.1 Age Categories

Age was measured as a continuous variable to quantify descriptive statistics including mean age between the groups (males, females, midazolam and propofol) and to estimate the linear component of the relationship between age and recovery time. Age was also placed into groups and measured categorically to explore the number of subjects in the midazolam and propofol group for each age group (Table 3.1).

Table 3.1 Age Categories (Depp & Juste, 2006)

Category	Age Range
Young	21 and under
Young Adult	22 - 34
Adult 35-44	35 - 44
Adult 45-54	45 - 54
Adult 55-64	55 - 64
Young-Old	65 - 74
Old-Old	75 - 84
Oldest-Old	85 - 99

Age categories were selected based on Depp and Juste's (2006) literature review of (28 studies) that explored risk factors for ill health among community-dwelling adults including: rates of morbidity, mortality, dependency and demands on health care services.

3.6.2 Body Mass Index (BMI)

BMI is a calculation of weight for height that has been defined by the World Health Organization (2013) (Table 3.2). This formula divides weight (in kilograms) by the square of the height (in meters) and the outcome value is used to classify individuals as follows:

Table 3.2 World Health Organization's BMI Classification

Classification	BMI
underweight	< 18.50
normal weight	18.50 – 24.99
overweight	25.00 – 29.99
Obese	≥ 30

As described in Chapter 2, body mass index (BMI) has been implicated in prolonged recovery time. Quadeer (2009) explored the incidence of hypoxia during 79 routine endoscopy procedures and reported it is more common in obese patients (≥ 30 kg/m^2) compared to non-obese patients (≤ 30 kg/m^2): 71% versus 46% respectively $p = 0.08$. Obese individuals have a higher incidence of obstructive sleep apnea (OSA) and only 10 – 20% of patients are aware they have this disorder (Villegas, 2004).

3.6.3 Medication History

When patients were admitted for colonoscopy an admission history was obtained, nurses recorded any medications patients were taking. For this study medication data were collected and collated into five categories (Table 3.3).

Table 3.3 Medication History Categories

Medication History	Medication History category
None	None
Medications not categorized as either cardiovascular medications or medications with sedative properties	Other
Cardiovascular medications and antihypertensives	Cardiovascular
Medications with sedative properties (including antipsychotic, anticonvulsant, antidepressant, antidiarrheal, antihistamine or opioid medications)	Sedative properties
Cardiovascular medications and those with sedative properties	Cardiovascular and sedative properties

3.6.4 Medical History

Nurses participating in the trial obtained medical history during the patient admission. The presence of co-morbid disease was extracted during data collection and six medical history categories were created based on the possible relationship / or risk for cardiopulmonary adverse events associated with sedation and analgesia (Table 3.4).

Table 3.4 Medical History Categories

Medical History	Medical History category
None	None
Other	Other
heart disease only	Heart Disease
heart disease and respiratory disease; heart disease and respiratory disease and other; respiratory disease and pelvic abdominal surgery; respiratory disease and pelvic abdominal disease and other; pelvic abdominal surgery and heart disease and respiratory disease; heart disease and pelvic abdominal surgery; heart disease and pelvic abdominal surgery and other; heart disease and respiratory disease and pelvic abdominal surgery and other	Heart Disease, Respiratory Disease, Pelvic Abdominal Surgery and Other
respiratory disease; respiratory disease and other	Respiratory Disease
pelvic abdominal surgery; pelvic abdominal surgery and other	Pelvic/Abdominal Surgery

3.6.5 Adverse Cardiopulmonary Events

Sedation-associated adverse events include hypoxemia, hypotension and cardiopulmonary complications, with hypoxemia being the most common (Meier, 2011;

Odom-Forren, 2008; Quadeer, 2009). The most widely used definition of hypoxemia is a severe episode of oxygen desaturation of less than 90% for 30 seconds (Cohen, 2008a; Gašparović et al., 2006; Rozario et al., 2008). Rozario (2008) reports desaturation and hypoxemia during endoscopic procedures are commonly attributed to hypoventilation induced by sedative agents. Hypotension is defined as a systolic blood pressure below 90 mmHg and requiring medical attention (Cohen, 2008a; Dumonceau et al., 2010; Sieg, 2007). Bradycardia is described as a heart rate of less than 60/min. and requiring medical attention (Cohen, 2008a; Day et al., 2011; Sieg, 2007; Ristikankare et al., 2000). Most hypoxic events are transient and respond swiftly to oxygen supplementation, however left untreated hypoxemia may contribute to more serious complications during colonoscopy (Quadeer et al., 2009).

In this study, sedation-related cardiopulmonary events were defined as oxygen saturation less than 90% with oxygen supplement, blood pressure less than 90mmHg systolic and 50 mmHg diastolic and requiring medical attention, bradycardia (heart rate less than 60 beats/minute) and requiring medical attention, the need for reversal agents, or respiratory assistance with airway interventions (Day et al., 2011; Dumonceau et al., 2010; Quadeer et al., 2009).

3.6.6 Modified Observer's Assessment of Alertness /Sedation Scale (MOAA/S)

While the sedation effect should end as the procedure ends, this is usually not the case and assessment of the patient's physical condition is extended through the recovery period (Aldrete, 1998). The MOAA/S (Table 3.5) is a tool used by nurses to assess the post procedural sedation recovery process and to identify when the patient can be safely discharged home (Aldrete, 1998; Dumonceau et al., 2010). In the study institution, the policy

for discharge home following procedural sedation requires that patients be assessed every 10 minutes. The nurse assesses the patients' respirations, circulation, level of consciousness, oxygen saturation and activity using the MOAA/S. When the total MOAA/S score is at least 8 out of 10 with respirations at 2 (indicating respirations are at a normal rate and the individual is able to breathe deeply and cough), the patient is considered recovered from sedation and ready for discharge. In this study, MOAA/S scores were used by nurses to identify when a patient was ready to be discharged.

Table 3.5 MOAA/S Scores

Score	Respirations	Circulation	Consciousness	O2 Sat	Activity
0	Apneic / Airway Management	BP < or > 50 mm HG or pre-procedure	Not responding or only responding to painful stimuli	SPO2 < 90% with O2 supplement	Unable to lift head or move extremities on command
1	Dyspnea or shallow irregular breathing	BP within 20-50 mm HG or pre-procedure	Responds to verbal stimuli but falls asleep readily	Requires O2 to maintain SPO2 > 90%	Weak movements
2	Normal rate, able to breath deeply and cough	BP within 20 mm HG of pre-procedure	Awake, alert and oriented to person, place and time	SPO2 > 92% on room air	Moves limbs purposefully as pre-procedure

3.7 Ethical Review

Prior to data collection, the researcher obtained ethical approval from the affiliated university and health authority Research Ethics Boards.

3.8 Protection of Data

Data were extracted from the 'procedural sedation record which is a regular part of the patients' health record. Because the associated data are not stored electronically (they are hand-written on this sedation record and scanned into a PDF document), it was necessary to extract the data from the patient chart manually. Personal identifiers such as name, social insurance number, date of birth, and personal health number (PHN) were removed from all

patient charts and each chart was assigned a numeric code (Subject 1, Subject 2, Subject 3, …). The researcher was the only individual who had access to identified health records during the processing and analysis of the data. Individuals involved with the study who were not employees of the health authority only had access to de-identified data. The anonymized paper research files were stored at the outpatient unit in a locked cupboard in the researcher's locked private office. The de-identified data were transferred to the SPSS file via a password protected flash drive and were analyzed at UBC.

3.9 Pre-procedure Patient Assessment

The physician assessed patients one week prior to the scheduled colonoscopy and performed a history and physical examination to reduce the potential for preventable complications during the procedure. A medical evaluation should be conducted prior to an endoscopic procedure where moderate to deep sedation is planned reduces the rate of sedation-related adverse events (Cohen et al., 2010). This assessment is intended to allow time for a history and physical examination and time to screen patients who will potentially have complications from sedation. It also allows the practitioner to identify target levels of sedation/analgesia, obtain informed consent, and to provide post-procedure instructions (Cohen et al., 2010; Wiggins et al., 2010). Furthermore, the patient's overall co-morbid disease risk can be classified according to the American Society for Anesthesiology (ASA) physical status classification during the visit (Table 3.5) (Wiggins et al., 2010). Only patients who were classified as ASA I (healthy subjects) – II (with at most minimal, well-controlled systemic medical problems), qualified for admission to this surgical outpatient unit. For those who qualified, the gastroenterologist discussed the risks and benefits of the two sedation

options (midazolam and propofol), and patients were invited to choose the sedation method they preferred.

3.10 Staff Training

The physician and nurses who participated in the pre-procedure, procedure, recovery and patient discharge process received training before the quality improvement project began. This training included: advanced cardiac life support (ACLS) training, online learning module for the Sedasys® System prepared by the vendor, a workshop on propofol presented by anesthesia and a review of the required patient assessment and documentation process. During ACLS training, the nurses and physician practiced necessary techniques to assist in avoiding sedation-related complications, reviewed patient monitoring skills and rescue measures necessary to manage adverse reactions. Upon completion of the training, nurses and physician were required to pass a written examination, an evaluation of their ability to use the Sedasys® System correctly, and an evaluation of their abilities to assess and manage a patient's airway complications. Practice standards, associated policies and clinical practice guidelines associated with the endoscopic procedure and the sedation and analgesia were reviewed with participants prior to the project start.

3.11 Sample, Inclusion/Exclusion Criteria and Sample Size

A convenience sample was obtained by reviewing health records over a five-month period in the surgical outpatient unit. All charts involving patients who had a colonoscopy performed by one physician with either midazolam and fentanyl or propofol and fentanyl administered intravenously for colonoscopy between May 25, 2012 and October 5, 2012 were selected. Charts were excluded if there was incomplete documentation.

An a-priori power analysis was performed using seven predictor variables (procedural sedation type (propofol or midazolam), age, sex, BMI, medical history, medication history and procedure time) that would predict recovery time. This analysis indicated that a sample size of 100 subjects in each group would be required, for a 2-tailed alpha of .05, a power of 0.8 to detect a medium effect size of 0.15, or 15% of the variability in the recovery time.

3.12 Measures

Table 3.6 shows the data extracted and units of measure for the study.

Table 3.6 Data Elements Extracted

Term	Unit of measure
Age	Age in years
Sex	Male, Female
Height	Height in centimeters or inches
Weight	Weight in kilograms or pounds
Medication history	Medication by name
Medical history	Medical condition by name
Sedation administered	Sedative agent by name
Opioid administered	Opioid agent by name
Procedure time	In minutes
Recovery time	In minutes
Total MOAA/S Score	At time 1, time 2, time 3, time 4
Individual MOAA/S Score time 1	Respirations time 1, Circulation time 1, Consciousness time 1, Oxygen saturation time 1,activity time 1
Individual MOAA/S Score time 2	Respirations time 2, Circulation time 2, Consciousness time 2, Oxygen saturation time 2,activity time 2
Individual MOAA/S Score time 3	Respirations time 3, Circulation time 3, Consciousness time 3, Oxygen saturation time 3,activity time 3
Individual MOAA/S Score time 4	Respirations time 4, Circulation time 4, Consciousness time 4, Oxygen saturation time 4,activity time 4

3.12.1 Procedure and Recovery Time

Procedure time was extracted from the patient record and was calculated from the following data points: time procedure started and time the colonoscope was withdrawn. Recovery time was calculated from the following data points: time of scope withdrawal to

time the patient assessed as ready for discharge based on an MOAA/S score greater than 8 with respirations at 2.

3.12.2 Sedation-related Cardiopulmonary Events

Table 3.7 shows categories of sedation-related cardiopulmonary events.

Table 3.7 Description of Cardiopulmonary Event

Cardiopulmonary Event	Description
⇓ Oxygen Saturation	<90% with oxygen supplementation
⇓ Blood pressure	<90mmHg systolic and 50mmHg diastolic and requiring medical assistance
⇓ Heart rate	<60 beats per minute and requiring medical assistance
Respiratory compromise	Use of reversal agents or respiratory assistance

3.13 Data Collection

3.13.1 Health Record Access and Selection

Patient charts were accessed using the Meditech® scheduling system. Charts were selected sequentially and when a chart was selected that did not have all data points documented, it was not used and the next sequential chart with complete documentation was selected until there were 200 charts with all data points documented: 100 charts with patients having received midazolam and 100 charts with patients having received propofol.

3.13.2 Equipment

Non-invasive blood pressure (NIBP) monitors are mounted at the head of each patient stretcher in the recovery area. Biomedical engineering dedicated two technicians to calibrate six NIBP monitors every seven days, and these monitors were marked and exclusively used for the trial. The monitors remained connected to electrical power during the entire trial period. All nurses involved in the study were trained to use a consistent method for measuring biophysiological parameters including: frequency of monitoring vital signs post

procedure, using a blood pressure cuff size appropriate to the patient, and correct placement of the pulse oximeter finger probe. Nurses were trained to record and document consistent time points for measuring recovery time and sedation-related cardiopulmonary status.

3.14 Data Analysis

Before data entry began, a codebook was created to outline the method for defining, labeling and assigning numerical values for study variables and missing data. All data were entered into an Excel file, which was imported into IBM's Statistical Package for the Social Sciences software (SPSS version 21 for Mac) analysis program. The researcher limited data entry sessions to two hours at a time to reduce errors. Ten charts were randomly selected from each sedation group (midazolam and propofol) were audited by the researcher to verify data entry accuracy. After data analysis and cleaning, data analysis was started using the SPSS version 21 for Mac and a p-value < 0.05 was considered significant. Normality of data sets was determined with SPSS Explore and Descriptive functions. Categorical variables are described with frequencies (percentages) and continuous variables are described with mean (standard deviation) or median (range) as appropriate. Stem and leaf plots and histograms were used according to their level of measurement to illustrate the data in a frequency distribution, to visualize the normality of the distribution and to assess for outliers (Cassidy, 2005; Pallant, 2010).

Several analyses were performed to examine differences between the two groups. First, comparisons between groups were made with parametric independent t-tests for continuous variables and ANOVAs and chi-squared analyses were used for exploring proportionality between cases and comparators including: type of sedation, age, sex, BMI, medical history, medication history, procedure length, duration of recovery and the frequency of sedation-

related cardiopulmonary events. Lack of statistical significance between variables was considered evidence that the variable demographics were similar across the groups.

If data met the assumptions for normal distribution they were placed in a multiple regression model to identify independent clinical predictors for duration of recovery from procedural sedation and analgesia and the incidence of sedation-related cardio-respiratory events. The statistical analyses were based on a significance level of 0.05 and a two-tailed test.

3.15 Issues of Rigor

The following were considered to be threats to internal and external validity in this study:

3.15.1 Threats to Internal Validity

Selection bias was identified as a potential threat to internal validity in this study because all charts with complete documentation where patients had a colonoscopy performed by the participating physician were selected. To minimize selection bias all participants were qualified using the same inclusion and exclusion criteria and charts were selected sequentially without an awareness of patient demographics. Measurement error bias was also identified as a threat to internal validity because there were a number of nurses involved in using the Sedasys® System, measuring recovery length and recording patient's biophysiological status. For the quality improvement project, the physician and the nurses were trained to use the Sedasys® System. The nurses were trained to use a consistent method for measuring biophysiological parameters: using the appropriate sized cuff for the patient, the correct placement of the finger pulse oximeter probe, and the frequency of monitoring vital signs post procedure. Regular audits were conducted and retraining was provided as

needed. Moreover, dedicated biomedical engineering technicians calibrated the NIBP monitors weekly.

3.15.2 Threats to External Validity

Study setting was identified as a threat to external validity. The study was conducted at only one site, yielding a high level of homogeneity in both the clinical procedure and the recording of data, therefore the findings cannot be generalized to other institutions as they may follow different protocols or have dissimilar patient populations. Moreover, patients who are seen at this outpatient unit are all classified as either ASA I or II, therefore the findings cannot be generalized to all patients who have procedural sedation during colonoscopy who are classified as ASA III or higher.

3.16 Summary

This chapter described the research design, the research questions and hypothesis, conceptual definitions, procedure, ethical considerations, patient assessment and staff training during the quality improvement project, sample, measures, data collection, health record acquisition process, equipment used, data management, statistical analysis and issues of rigor. The next chapter will discuss the study findings.

Chapter 4: Results

This chapter describes the findings of the study. It begins with a description of the sample demographic characteristics. Charts with missing data were excluded; therefore there were no missing values noted.

4.1 Sample Characteristics

The demographic characteristics of the sample are presented in Table 4.1. A total of 200 participants (100 in the midazolam group and 100 in the propofol group) who met the inclusion criteria were included in the study. The average age of the participants was 54.4 years (SD = 13) with the youngest participant being 19 years and the oldest 79 years. The majority of the sample was female (57%). The average age in the midazolam group was higher than that in the propofol group 58.9 years (SD = 12.1) versus 50.1 years (SD = 12.1), p=<0.001.

Age categories were selected to explore variation in risk as individuals' age. Participants in the midazolam group were generally older (ranged from 19 – 79 years) when compared with those in the propofol group (ranged from < 21 – 74 years). Participants in the propofol group generally had a lower BMI (87% with a BMI <30) when compared to the midazolam group (75% with a BMI <30). Participants in the propofol group appeared to be generally healthier than those in the midazolam group: 16% took no medication while 10% in the midazolam group did not take any medication and 9% participants in the propofol group took cardiac medications compared to 14% in the midazolam group. As well, significantly fewer participants in the propofol group had a co-existing medical history ($p = 0.015$) including cardiac or respiratory disease (22%) than those in midazolam group (32%).

Table 4.1 Characteristics of Study Participants for Midazolam and Propofol

Demographic Variables	All n = 200	Midazolam n = 100	Propofol n =100	*p*
Sex, n (%)				.668[a]
Male	86 (43)	41 (21)	45 (23)	
Female	114 (57)	59 (30)	55 (28)	
Age, mean in years (SD)	54 (13)	59 (12)	50 (12)	<.001[b]
Age groups, n (%)				<.001[a]
21 and under	2 (1)		2 (1)	
22 to 34	9 (5)	5 (3)	4 (2)	
35 to 44	5 (3)	2 (1)	3 (2)	
45 to 54	20 (10)	4 (2)	16 (8)	
55 to 64	30 (15)	15 (8)	15 (8)	
65 to 74	16 (8)	11 (6)	5 (3)	
75 to 84	4 (2)	4 (2)	0 (0)	
BMI, mean (SD)	26 (5)	27 (5)	26 (5)	.136[b]
BMI categories, n (%)				.294[a]
0.00 to 18.50	4 (2)	1 (1)	3 (3)	
18.51 to 24.99	82 (41)	37 (37)	45 (45)	
25.00 to 29.99	80 (40)	37 (37)	39 (39)	
30.00 and over	34 (17)	21 (21)	13 (13)	
Medication History, n (%)				.138[a]
None	52 (26)	20 (10)	32 (16)	
Other	57 (29)	30 (15)	27 (14)	
Cardiac	44 (22)	27 (14)	17 (9)	
Sedative	23 (12)	9 (5)	14 (7)	
Cardiac and Sedative	24 (12)	14 (7)	10 (5)	
Medical History, n (%)				.015a
None	68 (34)	30 (30)	38 (38)	
Other	35 (18)	10 (5)	25 (13)	
Heart Disease	47 (24)	27 (27)	20 (20)	
All	27 (14)	18 (9)	9 (5)	
Respiratory Disease	14 (7)	10 (5)	4 (2)	
Pelvic/Abdominal Surgery	9 (5)	5 (5)	4 (4)	

NOTE: a - Chi Square, b - Independent samples t-test
Medical history 'all' - Heart Disease, Respiratory Disease, Pelvic Abdominal Surgery and Other
BMI - Body Mass Index, SD – standard deviation

4.1.1 Demographic Information by Sex

The sample consisted of 43% males and 57% females with the midazolam group having a greater number of females (59%) than males (41%) and the propofol having slightly more females (55%) than males (45%) (Table 4.2).

A greater number of males (28%) than females (18%) took cardiovascular medications and this was consistent across both sedation groups: midazolam (males 39% versus females 19%, $p = .230$) and propofol (males 22% versus females 13%, $p = .279$). Across the sample there were more females than males who took medications with sedative properties (males 7% versus females 15%, $p = .061$). This was consistent across both sedation groups: midazolam (males 7% versus females 10%, $p = .230$) and propofol (males 7% versus females 20%, $p = .279$).

There were a greater proportion of males (32%) than females (36%) that had no medical history, and this differential was also evident in the propofol group (females 35% versus males 42%, $p = .031$). The sample had more males (33%) than females (17%, $p = .039$) who had a history of cardiac disease. This trend was not consistent across the two sedation groups: in the midazolam group there were more males (41%) than females (17%, $p = .031$) and in the propofol group there were fewer males (24%) than females (35%, $p = .392$) with a history of heart disease. There were a slightly higher proportion of males (12%) than females (8%, $p = .039$) who had a history of respiratory disease in the midazolam group.

Table 4.2 Characteristics of Study Participants by Sex and Sedation Group

	All (n = 200)		Midazolam (n = 100)		Propofol (n = 100)	
	Male (n = 86)	Female (n = 114)	Male (n = 41)	Female (n = 59)	Male (n = 45)	Female (n = 55)
Age, mean in years (SD)	55 (13)	54 (13)	59 (13)	59 (11)	52 (12)	49 (13)
	p =.610[b]		p =.961[b]		p = .311[b]	
Body Mass Index, mean (SD)	26 (5)	26 (4)	27 (6)	27 (4)	26 (5)	26 (4)
	p =.935[b]		p = .726[b]		p =.687[b]	
Medication History, n (%)						
None	24 (28)	28 (25)	8 (20)	12 (20)	16 (36)	16 (29)
Other	20 (23)	37 (32)	9 (22)	21 (36)	11 (24)	16 (29)
Cardiovascular	26 (30)	18 (16)	16 (39)	11 (19)	10 (22)	7 (13)
Sedative properties	6 (7)	17 (15)	3 (7)	6 (10)	3 (7)	11 (20)
Cardiovascular and sedative properties	10 (12)	14 (12)	5 (12)	9 (15)	5 (11)	5 (9)
	p = .061[a]		p =.230[a]		p =.279[a]	
Medical History, n (%)						
None	31 (36)	37 (32)	12 (30)	18 (32)	19 (42)	19 (35)
Other	9 (10)	26 (23)	2 (5)	8 (14)	7 (17)	18 (33)
Heart Disease	28 (33)	19 (17)	17 (41)	10 (17)	11 (24)	19 (35)
Heart Disease, Respiratory Disease, Pelvic Abdominal Surgery and Other	10 (12)	17 (15)	5 (12)	13 (22)	5 (11)	4 (7)
Respiratory Disease	6 (7)	8 (7)	5 (12)	5 (8)	1 (2)	3 (5)
Pelvic/Abdominal Surgery	2 (2)	7 (6)	0 (0)	5 (8)	2 (4)	2 (4)
	p = .039[a]		p =.031[a]		p =.392[a]	

a Chi-square b Independent t-test

4.2 Recovery Time and Procedure Time by Sex and by Sedation Group

The average procedure length was slightly longer for participants who received midazolam than for those who received propofol during colonoscopy (23 minutes, SD = 9 versus 20 minutes, SD = 8; p = .017) (Table 4.3). Recovery time was significantly shorter in the propofol group with an average length of 10 minutes (SD = 8) than in the midazolam

group (19 minutes, SD = 9), p = <.001. There was minimal difference in procedure time and recovery time between males and females in the two sedation groups (Table 4.4).

Table 4.3 Recovery Time and Procedure Time for Midazolam or Propofol

	All (n = 200)	Midazolam (n = 100)	Propofol (n = 100)	*p*
Procedure time in minutes, mean (SD)	21 (8)	23 (9)	20 (8)	.017[a]
Recovery time in minutes, mean (SD)	15 (10)	19 (9)	10 (8)	<.001[a]

a Independent t-test

Table 4.4 Recovery Time and Procedure Time by Sex and by Propofol and Midazolam

	All (n = 200)		Propofol (n = 100)		Midazolam (n = 100)		*p*
	Male (n = 86)	Female (n = 114)	Male (n = 45)	Female (n = 55)	Male (n= 41)	Female (n = 59)	
Procedure time in minutes, mean (SD)	22 (9)	21 (7)	19 (8)	20 (7)	24 (10)	22 (8)	.044[a]
Recovery time in minutes, mean (SD)	15 (10)	15 (9)	10 (10)	11 (7)	19 (9)	19 (9)	<.001

a 2-way ANOVA

4.3 Predictors of Recovery Time

Multiple regression analysis was used to assess the contribution of each of the following independent variables: age, BMI, sex, type of sedation (propofol or midazolam) and medical history, to predict recovery time after controlling for the influence of the remaining variables. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity.

Table 4.5 Regression Model Predicting Recovery Time

	Recovery Time			
Predictor Variable	Unstandardized B (95% CI)	SE	ß	*p*
Age	-.021 (-.13, .09)	.055	-.028	.71
BMI	-.077 (-.34, .19)	.134	-.038	.56
Sex	-.006 (-.01, .02)	.009	.042	.52
Propofol	-9.32 (-11.99, -6.65)	1.35	-0.48	<.0001*
Medical History				
Heart Disease	0.61 (-2.86, 4.09)	1.76	0.03	.73
Respiratory Disease	-1.14 (-6.31, 4.04)	2.63	-0.03	.67
PAS	2.47 (-3.67, 8.60)	3.11	-0.05	.43
Other	1.91 (-1.78, 5.60)	1.87	0.08	.31
All	0.53 (-3.66, 4.72)	2.12	0.02	.80

R-squared = 0.22

*. Coefficient is significant at < .05 level (2 tailed); PAS – pelvic abdominal surgery

The total variance explained by the full model was 22% (R^2=0.22, F (9,189) = 6.05, p = <0.001. Propofol provided the largest contribution to the variance in recovery time (β=-0.48, p=<0.0001), after controlling for age, BMI, sex, and medical history (Table 4.5).

4.4 Detailed MOAA/S Score by Midazolam and Propofol

Recovery began once the colonoscope was withdrawn. Biophysiological monitoring (circulation, respirations, level of consciousness, oxygen saturation and activity) was measured every ten minutes during the recovery period and scores were rated using the MOAA/S score (Table 3.6). There were no participants in the midazolam group that scored 0 for circulation (indicating their blood pressure measured more or less than 50 mmHg from baseline) although one participant scored a 0 at time point 1 in the propofol group. Participants scored generally lower in the midazolam group, most notably at time point 1; In the midazolam group, 38% scored "2" for level of consciousness at time point one compared to 78% in the propofol group. Similarly, 78% in the midazolam group scored "2" for oxygen saturation at time point 1, compared to 98% in the propofol group. Moreover, there were no

participants in the midazolam group that scored “2” for activity at time point 1 while 7% in the propofol scored “2” in this category at time point 1.

4.5 Total MOAA/S Score by Midazolam and Propofol

Individual scores were added and the total MOAA/S Score was documented for each of the 4 time points (Table 4.6). At time point 1, participants in the propofol group recovered significantly faster than those in the midazolam group ($p = <.001$). Twice as many participants in the propofol group (60%) than the midazolam group (30%) scored “9” at time point 1. Moreover, six participants in the propofol group scored “10” at time point 1, compared to no scores of 10 in the midazolam group.

To satisfy the facility’s criteria for discharge home, participants require a total score of 8 with respirations a 2. Participants in the propofol group were discharged home earlier: at time point 2, 45% in the propofol group were discharged home compared to 7% in the midazolam group; at time point 3, 96% in the propofol group were discharged home while only 39% in the midazolam group were discharged.

Table 4.6 Total MOAA/S Score at Times 1-4 by Midazolam and Propofol

Time Point	MOAA/S Score	Midazolam n (%)	Propofol n (%)	*p*
1	6	3 (3)	--	<.001[a]
	7	26 (26)	6 (6)	
	8	41 (41)	28 (28)	
	9	30 (30)	60 (60)	
	10	--	6 (6)	
	Home	--	--	
2	6	--	--	0.11[a]
	7	5 (5)	--	
	8	22 (22)	6 (6)	
	9	49 (49)	33 (33)	
	10	17 (17)	10 (10)	
	Home	7 (7)	45 (45)	
3	6	--	--	0.80 [a]
	7	--	--	
	8	4 (4)	--	
	9	37 (37)	3 (3)	
	10	20 (20)	1 (1)	
	Home	39 (39)	96 (96)	
4	6	--	--	0.66 [a]
	7	--	--	
	8	--	--	
	9	5 (5)	1 (1)	
	10	1 (1)	--	
	Home	94 (94)	99 (99)	

a Chi-square

4.6 Summary

Variables including: age, sex, gender, medical history medication history, procedure time and sedative agent were hypothesized to influence recovery time and the incidence of sedation-related cardiopulmomary events among patients having a colonoscopy. The sedative agent (midazolam or propofol) was the only parameter that resulted in a significant difference in recovery time.

Chapter 5: Discussion

In chapter five, the purpose of the study is reviewed and the primary findings are discussed within the context of the literature, the research questions, and in relation to the study's theoretical framework.

5.1 Purpose of the Study

As colorectal cancer screening programs develop, capacity to support existing resources for colonoscopy may become increasingly challenged. Procedural sedation recovery is a lengthy part of the overall colonoscopy procedure and is sometimes unpredictable. The patient receiving moderate sedation has the potential to move into deep sedation and the further the sedation depth progresses along the continuum, the complication risk increases and the recovery time extends. The primary concern for procedural sedation internationally is to reduce the risk for sedation-related complications that lead to adverse events, however identifying changes to current endoscopy practice that adds efficiency could result in improved access to resources required. This study aimed to explore differences in recovery time and sedation-related cardiopulmonary events between patients who had midazolam versus propofol for procedural sedation during colonoscopy. It also examined the relationship between procedure length and recovery time across the two groups who received these difference sedatives and explored the influence of sex, age, BMI, procedure length and medical history on patient outcomes.

5.2 Discussion of Findings

In this section, the findings are discussed in relation to the research questions, the literature and the theoretical framework. Limitations of the research and recommendations for future research are also discussed.

5.2.1 Overview of the Findings

There were a greater number of females (57%) than males (43%). Subjects in propofol group were somewhat younger and healthier than those in the midazolam group (subjects had fewer comorbid conditions including cardiac and respiratory disease, took fewer cardiac medications and had a generally lower BMI). Although the procedure time was slightly shorter for those who had propofol, the reduction in recovery time was statistically significant (p = <.001) for those who received propofol for procedural sedation. There were no sedation-related adverse events across the study.

5.2.2 Findings in Relationship to the Research Questions

The study findings illustrate the sedative agent (propofol) used for procedural sedation during colonoscopy is the largest contributor to the difference in recovery time between the two sedation groups, with a shorter recovery time (10 minutes, SD = 8 minutes) versus (19 minutes, SD 9 minutes) for those in the midazolam group. The mean procedure length (20 minutes) in the propofol group was less that in the midazolam group (23 minutes), however it was not statistically significant. Age, sex, medication history, medical history and BMI did not significantly influence the length of recovery or the incidence of sedation-related cardiopulmonary events.

Further analysis examined the times when subjects met the assessment criteria for discharge home using the detailed MOAA/S measurement tool. Results demonstrated subjects in the propofol group were discharged home sooner than those in the propofol group (45% of patients were discharged 10 minutes after procedure completion in the propofol group versus 7% in the midazolam group and 96% in the propofol group were discharged 20 minutes after the procedure versus 39% in the midazolam group).

5.2.3 Findings in Relationship to the Literature

This study's results which demonstrated a reduced recovery time when propofol was administered for colonoscopy are consistent with existing research. Ulmer et al. (2003) undertook a study that reported a significant reduction in recovery time following procedural sedation during colonoscopy (16.5 minutes for propofol versus 27.5 minutes for midazolam).

Singh et al. (2008) conducted a systematic review of randomized control trials around the world comparing the efficacy and safety of propofol to traditional agents (narcotics and/or benzodiazepines) for sedation during colonoscopy between January 1980 and June 2007. While 22 studies met the inclusion criteria for the above objective, only four were considered for the following reasons: study quality was not consistent, the definition and criteria for determining outcomes varied, and some studies evaluated propofol combined with another agent rather than propofol alone, therefore not relative as a comparison to this study. These studies compared midazolam to propofol for colonoscopy and explored variables similar to the variables in this study (recovery time and safety). The researchers reported a statistically significant reduction in recovery time when propofol was used for procedural sedation during colonoscopy (-14.68 minutes, CI: -19.79 to -9.58 minutes) (Singh et al., 2008). Two of these studies were conducted in Switzerland in 2003 and 2005, and the other two in the United States in 2002 and 2003. This study adds to the growing body of evidence that propofol used for colonoscopy leads to a faster full recovery.

Limited research has explored differences in procedure duration when comparing propofol to midazolam for colonoscopy and results in this study are similar to published results. In a systematic review of the literature, two US studies (n = 168) explored procedure

time between patients having either midazolam or propofol for sedation during colonoscopy and reported no significant mean difference in procedure duration (-1.98 minutes, 95% CI: -6.12-2.17 minutes) (Singh et al., 2008).

The incidence of sedation-related cardiopulmonary events reported in this study were also consistent with results from other research. A meta-analyses of randomized controlled trials comparing propofol to midazolam reported no significant difference in the incidence of hypoxemia across the two groups (McQuaid et al., 2008). In a systematic review (Singh et al., 2008), two Swiss studies and two USA studies explored the incidence of hypoxia and apnea among those who had propofol and those who had midazolam during colonoscopy (n = 407). Researchers reported there was no statistically significant difference in the incidence of these sedation-related adverse events (OR 0.69, 95% CI: 0.25-1.89). Two of these studies explored the incidence of hypotension across the two sedation groups and reported no significant difference in the incidence of hypotension (OR 1.03, 95% CI: 0.28-3.83) (Singh et al., 2008). Twelve studies included in a meta-analysis reported no significant difference in the incidence of adverse events when comparing outcomes of sedation using propofol and midazolam (Quadeer et al., 2005). This study has shown similar results to other studies when comparing midazolam to propofol for colonoscopy. Although research has explored sedation and safety, detailed comparison is often difficult for several reasons: a consensus on optimal dosing strategies does not exist; various sedative and analgesia agents are used; and the definition of sedation-related complications is not consistent among practitioners (Miner & Krauss, 2007).

The dosing and timing of manual administration of sedatives is also difficult to compare because multiple confounding variables exist: the patient's response to pain and the

clinician's tolerance for under or over sedation (Miner et al., 2007). Moreover, the target depth of sedation is operator dependent and not clearly defined and it is varies between practitioners. Because the administration technique and goals of the endoscopist affect the potential for an adverse event, defining the differences in complication rates is challenging at best.

This study found age did not significantly influence recovery duration or sedation-related adverse events. Sharma et al. (2007) reported age was a significant predictor of cardiopulmonary events, although it did include all endoscopic procedures, higher acuity inpatients and outpatients and had no cap on age. While the results in the Sharma study are contradictory to the results in this study, it must be noted that this study included only outpatients with an ASA of I or II and an upper age limit of 79 years who had a colonoscopy and did not include patients who had complex endoscopic procedures. Quadeer (2009) also reported the incidence of hypoxia to be greater among patients ≥ 60 years, however the study was not exclusive to colonoscopy and therefore may have included patients who had endoscopic procedures with greater risk. A third study reported a higher incidence of sedation-related cardiovascular events among older patients who had colonoscopy, however this study did not define the sedation / analgesia used (Day et al., 2011).

When exploring the relationship of BMI and cardiopulmonary events, this study was not consistent with other studies. Quadeer (2009) reported BMI was a significant predictor of the incidence of unplanned sedation-related adverse events ($p = 0.04$) however the study an alternate opioid agent was used.

To my knowledge, this is the first Canadian study that examined the procedural sedation recovery process in detail using the MOAA/S. Moreover, there have not been any

studies where these outcomes were explored when propofol was administered using a computer-assisted sedation-administration system. Two US studies (n = 89 and n = 100 respectively) explored variations in the recovery process for patients who had either midazolam or propofol during outpatient colonoscopy (Sipe et al., 2002 and Sipe et al., 2007). The findings from the study are consistent with this research and therefore the results add to the safety measurement with these medications.

5.2.4 Findings in Relationship to the Theoretical Framework

Timely access to diagnostic endoscopic services and screening for colorectal cancer was instrumental in the decision to proceed with this study. Recovery from sedation and analgesia is a lengthy part of the overall process for colonoscopy and therefore identifying changes that improve efficiency could result in improved access to care.

Existing research associated with evidence-based sedation and analgesia alternatives for colonoscopy was explored and compared to practice on this endoscopy unit and a gap between current evidence and knowledge use among endoscopy clinicians in this setting was identified. Latimer's (2010) conceptual model, KUPC, was used to link theory and evidence to clinical decision-making and subsequently clinical outcomes from both a clinical and administrative perspective, in order to identify activities that could be used to improve efficiencies and enhance patient care during colonoscopy.

The KUCP model suggests that clinical expertise influences patient outcomes. Before the trial began, experienced endoscopy registered nurses were offered an opportunity to participate and were provided with the trial guidelines, extensive education, resources, and ACLS certification. Additional training associated with pharmacology and cardiopulmonary risk aligns with safe sedation practice recommendations.

Patient characteristics that had the potential to influence recovery time and the incidence of sedation-related cardiopulmonary events were identified in the literature and were defined in the study methodology. The literature reported patient gender-related pharmacokinetic differences among men and women (variances in body weight, organ size, gastric motility and renal filtration) can alter drug metabolism, therefore sex was explored in relation to the study variables. Advancing age was also associated with risk and was therefore explored in this study. Age categories were selected as outlined in a recent publication on successful aging and factors associated with aspects of aging that presented the greatest risk were identified. The literature also reported that an increased BMI may be associated with sedation-related cardiovascular risk. BMI categories were defined as outlined in the World Health Organizations global database (World Health Organization, 2004). Increased patient acuity can increase risk for cardiovascular events, therefore medical history and medication history were explored. Patients admitted to this facility were screened for medical risk and admission was restricted to patients who were classified as ASA I or ASA II. The findings in this study were consistent with other studies in that sex, age, BMI, medical history and medication history did not significantly influence recovery time.

Organizational factors were considered prior to this retrospective chart audit. Health records approval to access health records was obtained. Consistent data abstraction parameters (for sedation-related adverse events and procedure recovery) were identified in the literature and outlined in the study methodology.

Sociopolitical factors were also considered in the study methodology. Ethics approval was obtained from the affiliated university and from the health authority's Research Ethics Board. Moreover, the researcher abided by the health authority's policy detailing data

protection and patient confidentiality. The health authority's guidelines and national standards for procedural sedation and recovery (including ASA classification risk assessment, patient monitoring requirements using MOAA/S assessment and Aldrete scoring tool) were used to develop study methodology.

5.3 Limitations of the Study

The study was conducted in a single endoscopy unit in an urban Canadian health authority with one physician who performed colonoscopy on otherwise healthy patients who were either ASA I and II. The physician assessed patients who were referred for colonoscopy in the office prior to the procedure and offered healthier patients (fewer co-morbidities and slightly younger) the opportunity to participate in the propofol trial. In general practice a mix of a variety of endoscopic inpatient and outpatient procedures may be performed on patients with an ASA I-IV and therefore results in this type of setting may vary depending on the mix of procedures. This sample is then not reflective for all patients in all acute care endoscopy units and its external validity is limited.

Propofol was administered via the Sedasys® System and subjects in this group were monitored for end tidal CO_2, while those in the midazolam group were not. One must consider whether the number of cardio-respiratory events may be influenced by the fact that measuring end tidal CO_2 with this device may have contributed to earlier recognition of respiratory status than the current manual administration monitoring oxygen saturation.

The potential for measurement bias exists with a retrospective study as RNs in the recovery area may have inconsistently assessed patient's physical readiness for discharge during the trial.

Data extraction was completed by one abstractor, however this individual was aware of the hypothesis, therefore reviewer bias must also be considered.

5.4 Implications for Nursing Practice

This study found an alternate sedation to what is traditionally used on this unit resulted in a statistically significant reduction in recovery time during colonoscopy. Prior to the trial, endoscopy nurses expressed ongoing concerns that patients were often excessively sedated. These nurses willingly accepted the opportunity to participate in the trial to compare sedative and analgesia options in an effort to improve patient care.

Current sedation practice does not require RNs to have ACLS training, however if propofol were to be adopted for use, all RNs working in the endoscopy unit would require ACLS certification. Because propofol has a very short time to peak effect and allows for rapid awakening after administration, nurses may not experience the stress they currently describe as patients frequently present showing signs of deeper sedation levels following midazolam administration. If propofol was administered using a "closed-loop" system that incorporates a real-time measure of drug effect designed to maintain a minimal to moderate sedation level, consistence may improve confidence among the endoscopy nurses. Nurses typically prefer not to challenge a physician's sedation practice, therefore if propofol was administered using this device, standard dosing would remove the barrier between physicians and nurses, perhaps influencing a more collaborative culture.

5.5 Implications for Nursing Policy

Currently, human resources vary in the endoscopy setting from site to site. Some units have two RNs in the procedure during the procedure; one to monitor the patient and one to assist with the procedure. Others have one RN performing both duties. Standard patient

monitoring includes: blood pressure, pulse, respirations and oxygen saturation. Additional monitoring including assessment of cardiac status varies across the sites. In some sites cardiac status is monitored for all patients, some areas only assess cardiac status for patients who have a cardiac history or are undergoing complex endoscopic procedures, and others do not monitor cardiac status for any patients.

Because of the potential risks associated with propofol, it has been suggested an anesthetist be available to support the patient during propofol administration. This practice is expensive and research over the last decade has reported propofol can be given safely in smaller doses. Creative changes to endoscopy staffing (e.g. anesthetic assistants, nurses, nurse anesthetists) may address risk and support efficiencies related to propofol use.

Endoscopy skills for nurses are not included in basic nursing education and are also not standardized across sites. Education typically involves mentorship by an experienced RN in the endoscopy suite and is supported by site-specific procedural sedation and analgesia guidelines. Some vendors associated with endoscopy equipment provide equipment specific training, and the Canadian Society of Gastroenterology and Nurses and Associates and Society of Gastroenterology Nurses and Associates, Inc. in the United States publish position statements and guidelines to support endoscopy practice, although education and practice is inconsistent across the province of British Columbia. This health authority is currently developing a standard guideline to support procedural sedation practice and the development of standardized endoscopy education would promote in consistent practice across the region. If physicians were involved in the education, it would support collaboration across this specialty. Studies have reported the adoption of evidence-based practice among nursing staff is greater with improved collaboration between physicians and nurses and when patient

acuity is increased (Latimer et al. 2010), therefore adequate education to support the use of propofol may influence the delivery of collaborative and evidence-based endoscopy care by nurses.

This health authority currently collects very little data associated with procedural sedation and data that are captured are not consistent across the sites. Standardized guidelines, education, and procedural and sedation documentation would result in consistent data, which in turn would improve care and patient outcomes.

Results from this study suggest colonoscopy sedation recovery time can be reduced safely. If endoscopy capacity challenges are to be managed, innovative and efficient methodologies to optimize resources including regional standardized endoscopy education, improved documentation and consistent data collection should be employed.

5.6 Implications for Future Research

Extensive research has compared the use of propofol to traditional sedative agents including benzodiazepines for colonoscopy however limitations in research methodology needs to be identified and addressed. Many have also explored the influence of specific patient characteristics, including age, BMI, sex and co-morbid conditions, although measurement of these predictors on both recovery and the incidence of sedation-related adverse events has not been consistent and further safety and operational efficiency research is essential. Ethnic variations in drug metabolism has not been widely explored and further investigation would be useful to examine the relationship between ethnicity and the provision of procedural sedation and analgesia as it relates to recovery times and cardiopulmonary risk within the endoscopy setting.

5.7 Summary and Conclusions.

Guided by previous research and using Latimer's Knowledge Use in Pain Care theoretical framework, this study was conducted to explore alternate options to the traditional sedation and analgesia regime for colonoscopy in this surgical outpatient endoscopy unit. All factors considered during the trial associated with the provision of care during colonoscopy were examined. A retrospective chart review was used to examine the difference in recovery time and the incidence of sedation-related adverse events between patients who had either midazolam or propofol while controlling for sex, age, BMI, and medical history. There was a statistically significant reduction in recovery time when propofol was used when compared to midazolam.

Patient sedation for endoscopy is evolving throughout the world and this is attributed to a rapid increase in demand for endoscopic services and economic pressures associated with the quest to maintain service levels. New sedation options and methods of administering and monitoring sedative agents are essential to maintain current capacity challenges. The results of this study suggest that alternate sedation options might be used safely for colonoscopy in this population.

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Appendix A – ASA Classification

American Society of Anesthesiologists (ASA) Classification Class Description

Class	Description
ASA I	A normal healthy patient (eg. Healthy patient without any systemic medical problems other than that related to procedure).
ASA II	A patient with mild systemic disease (eg. Patient who smokes and has hypertension, which is well controlled).
ASA III	A patient with severe systemic disease (eg. Patient with diabetes and angina. Takes medications, including insulin. Angina - fairly stable).
ASA IV	A patient with severe systemic disease that is a constant threat to life (eg. Patient with diabetes, angina and congestive heart failure. Patient has dyspnea on mild exertion and chest pain).
ASA V	The moribund patient who is not expected to survive 24 hours with or without the procedure.