In compliance with the
Canadian Privacy Legislation
some supporting forms
may have been removed from
this dissertation.

While these forms may be included
in the document page count,
their removal does not represent
any loss of content from the dissertation.

THE SAFETY AND EFFICACY OF A POLICY OF SEDATION VERSUS NO SEDATION IN THE PERFORMANCE OF UPPER GASTROINTESTINAL ENDOSCOPY: A RANDOMIZED CONTROLLED TRIAL

Neena S. Abraham MD, FRCP(C)

Department of Epidemiology and Biostatistics

McGill University, Montréal

October 2002

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of MSc.

Your file Votre référence
ISBN: 0-612-88141-5
Our file Notre référence
ISBN: 0-612-88141-5

ABSTRACT

Background: Esophagogastroduodenal endoscopy (EGDE) is the most commonly performed endoscopic procedure in Canada and represents 51-65% of all gastrointestinal procedures performed in teaching hospitals. The routine use of conscious sedation during EGDE has facilitated its diffusion, ensured patient and physician satisfaction and has increased the potential risk of cardiorespiratory morbidity. It remains unclear if all adult ambulatory patients require routine conscious sedation prior to diagnostic EGDE, as the efficacy and safety of such a policy has not been rigorously studied in a North American population.

Methods: Patients were randomly assigned to sedation or placebo in a double-blind trial. The main outcome measure was "successful endoscopy"—a composite score of the physician's rating of technical adequacy (1= inadequate to 4= totally adequate) and the patient's satisfaction immediately after the procedure (1= acceptable to 5= unacceptable). Secondary outcomes included the patient's satisfaction with their level of comfort and willingness to repeat EGDE under similar test conditions. Patient covariates that were investigated as confounders/effect modifiers included demographics (age, gender, race), previous experience with endoscopy, expectations of endoscopy and anxiety. Analysis was completed using an intention to treat approach. The present analysis is an interim analysis based on 63% of the patients required.

Results: So far 360 patients of the anticipated patients have been enrolled, (182 randomized to sedation, 178 randomized to placebo). Groups were similar for all

baseline characteristics. The mean age was 54.2 years (SD: 16 yrs), 51% were female and 61.4% of procedures were "successful" (83% active vs. 39% placebo). 98% of procedures were technically adequate (99% active vs. 97% placebo). Eighty-one percent of patients randomized to placebo were able to complete EGDE without sedation. The major determinant of "successful endoscopy" was the use of sedation (OR= 7.52; 95% CI: 4.61-12.26). Sixty-one percent of patients reported satisfaction with their level of comfort during the EGDE. The strongest predictor of patient satisfaction alone was randomization to sedation (OR 9.53; 95% CI: 4.55-19.96). Seventy-two percent of patients were willing to repeat their procedure under similar test conditions. The strongest predictor of a patient's willingness to repeat the procedure was randomization to sedation (OR= 3.84; 95% CI: 2.3-6.4). Preliminary subgroup analysis suggested that among patients greater than 55 yrs and with decreased pharyngeal sensitivity, there was a greater likelihood of successful unsedated endoscopy, when compared to other subsets (45% successful vs. 39% successful among the unstratified placebo population; 98% power).

Conclusion: The use of sedation does not improve technical adequacy. However, the use of sedation in the performance of EGDE is the strongest predictor of a successful endoscopy, patient self-reported satisfaction and willingness to repeat the procedure.

ABRÉGÉ

Historique: L'endoscopie oesophago-gastroduodénale (EOGD) est l'endoscopie la plus fréquente au Canada et représente 51-65% de toutes les procédures gastro-intestinales faites dans les hôpitaux d'enseignement. L'utilisation de la sédation pendant une EOGD a facilité la diffusion de ces tests et a assuré la satisfaction du patient ainsi que du médecin. Par contre ceci a aussi augmenté le risque potentiel de morbidité cardio-respiratoire. Il n'est toujours pas clair si tous les bénéficiaires adultes ambulatoires ont besoin de sédation pendant un EOGD car l'efficacité et la sécurité de ce genre d'approche n'ont pas encore été étudiés rigoureusement dans une population Nord-Américaine.

Méthode : Des bénéficiaires ont été randomisés pour recevoir soit une sédation ou un placebo dans cette étude à double insu. Le résultat principal était une « endoscopie réussie » qui consistait d'un score établi par l'opinion du médecin sur la technique (1=inadéquate à 4= totalement adéquate) et la satisfaction immédiate du bénéficiaire après l'endoscopie (1=acceptable à 5=inacceptable). Les résultats secondaires incluent la satisfaction du bénéficiaire, son niveau de confort ainsi que la volonté de répéter l'EOGD dans les mêmes circonstances. Les autres variables qui on été regardées comme modificateurs possibles étaient les données démographiques (age, sex, race), l'expérience,antécédent avec endoscopie, l' attente du bénéficiaire pour l'endoscopie et l'anxiété. L'analyse

était accomplis en utilisant une approche « intention to treat ». La présente analyse est une analyse préliminaire basée sur 63% des patients requis.

Résultats : À date, 360 bénéficiaires ont été randomisés (182 à la sédation et 178 au placebo). Les deux groupes sont similaires pour toutes les caractéristiques de base. L'âge moyen était de 54.2 années (DS : 16 ans). 51% étaient des femmes et 61.4% des endoscopies étaient réussies (83% active vs 39% placebo). 98% des procédures étaient techniquement adéquates (99% active vs 97% placebo). 81% des bénéficiaires randomisés à recevoir le placebo étaient capables de compléter l'EOGD sans sédation. Le déterminant majeur d'une endoscopie réussie était l'utilisation de la sédation (OR=7.52; 95% CI :4.61-12.26). 61% des bénéficiaires étaient satisfaits de leur niveau de confort pendant l'EOGD. L'association la plus forte avec la satisfaction de bénéficiaire était l'utilisation de sédation (OR=3.84; 95% CI : 4.55-19.96). 72% des bénéficiaires referaient leur endoscopie dans les mêmes conditions. L'association la plus forte avec la volonté du bénéficiaire de refaire l'endoscopie dans les même conditions était la sédation. (OR=3.84; 95%CI : 2.3-6.4). L'analyse préliminaire des sous-groupes a démontré que les bénéficiaires âgé de plus de 55 ans et avec une sensitivité pharyngeale diminuée avaient une plus grande chance d'avoir une endoscopie réussie sans sédation (45% réussite vs 39% réussite dans les groupes non stratifiés de placebo; puissance 98%).

Conclusion : L'utilisation de la sédation n'a pas amélioré la technique de la procédure. Par contre, la sédation était le facteur le plus associé avec une

endoscopie réussie, la satisfaction du bénéficiaire et la volonté de répéter la procédure dans les mêmes circonstances.

TABLE OF CONTENTS

4. THE RANDOMIZED CONTROLLED TRIAL

4.1 Study justification

4.2 Study objectives and hypothesis

4.3 Methods

4.3.1 Study design

4.3.2 Study population

4.3.3 Study outcomes

4.3.4 Randomization

4.3.5 Study interventions

4.3.6 Possible confounders and effect modifiers

4.3.7 Data collection procedure

4.3.8 Blinding/unblinding procedure

4.3.9 Sample size and power estimate

4.3.10 Statistical analysis

4.3.11 Ethical considerations

4.4 Results

4.4.1 Patient population

4.4.2 Correlation between variables

4.4.3 Predictors of "successful endoscopy"

4.4.4 Subgroup Analysis (Effect Modifiers of "successful endoscopy")

4.4.5 Multivariate Model of "successful endoscopy"

4.4.6 Other Outcomes

1. STATEMENT OF ORIGINALITY

The review of the literature and data collection presented in this thesis is the original work of the author, funded by a grant from the Canadian Association of Gastroenterology, Carsen Industries and the Medical Research Council of Canada awarded to the candidate for the completion of her Masters programme. The candidate independently performed the literature review, data clean-up, analysis and data synthesis/interpretation. The protocol and data abstraction forms was the work of a research group at McGill University led by the candidate's co-supervisor, Dr. Alan Barkun, with which the candidate was affiliated as an active member.

The main study described in this thesis represents an original, as yet unpublished contribution to the field of gastroenterology and endoscopy. The author has presented portions of this study, in abstract form, at the Digestive Diseases Week, San Diego, California, and May 2000 and at the Digestive Diseases Week, San Francisco, California, May 2002.

1. INTRODUCTION

Upper gastrointestinal esophagogastroduodenal endoscopy (EGDE) is carried out for a multitude of clinical indications (1). It is the most commonly performed endoscopic procedure with an incidence of about 8.6 per thousand population (2), and in Canada represents 51-65% of all gastrointestinal (GI) endoscopic procedures performed in teaching hospitals (3). The use of conscious sedation has resulted in the widespread diffusion and acceptance of this technology (4).

Conscious sedation implies the administration of medications that allow the introduction and manipulation of the gastroscope, yet provide a relaxed patient, able to respond and maintain vital functions. Its use has resulted in a high degree of satisfaction, expressed by both patients and physicians (5). However, this increased patient and physician satisfaction is counter-balanced by the increased morbidity and mortality associated with the use of conscious sedation (6), and the increased up-front costs to the health care system (7).

At the present time, there exist no clinical practice guidelines to recommend who should receive sedation when undergoing an EGDE. Both a Canadian consensus conference (8) and an American survey (9) suggested that the majority of the gastroenterologists in North America administer sedation when performing routine diagnostic EGDE. However, preliminary and uncontrolled data in other populations including Scandinavia, Britain, Japan and Iraq, suggest that large subgroups of patients can comfortably undergo an EGDE

with only local pharyngeal anesthesia (4, 10, 11-13). A rigorous, controlled experimental examination of the efficacy of diagnostic EGDE performed with and without standard parenteral sedation in a typical North American adult ambulatory population is a critical first step to establish whether a difference in effectiveness exists between these two strategies.

This thesis reviews the international data collected thus far on the performance of the sedated and unsedated diagnostic EGDE. Furthermore, the randomized controlled trial presented attempts to quantify important endoscopic clinical outcomes that may differ between the two groups (those patients who undergo EGDE with sedation, and those who undergo the procedure without sedation), and attempts to identify, in a preliminary fashion, possible differences between subgroups of patients.

At the end of ten months of enrollment (June 1999-March 2000), only 63% of our total sample size had been randomized. It was anticipated that to achieve our total sample size, at least one additional year of resources were required to invest. Thus this interim analysis was conducted to determine final disposition of the trial.

3. LITERATURE REVIEW

3.1 Endoscopy

3.1.1 Historical Perspective and Evolution of the Technology

The earliest human description of upper abdominal discomfort was termed "dyspepsia" by the Greek physician Hippocrates. (14) However, his search for the pathogenesis of this discomfort was limited to the external examination of the human body by an inability to seek within the body's cavity. Medical curiosity then led early physicians and scientists to seek methods to examine within the human body. In 1868, the nineteenth century physician Kussmaul consulted sword-swallowers and ancient anatomic descriptions of the digestive tract to develop the first "swallowing tube", which ingeniously permitted a limited but tantalizing view of the upper digestive tract.

Collaboration among surgeons and optical engineers in the Austro-Hungarian Empire led to the evolution of the first usable gastroscope by Mikulicz in 1881(14). Prior to the 20th century, key limitations in this technology included rudimentary optical lens technology, poor illumination, a lack of flexible devices, and the inability to control secretions. Later, the German clinician and mathematician Rudolf Schindler developed the first semi-flexible gastroscope with noted German engineer R. Wolf in 1932, and following his escape from Nazi Germany, established the American Gastroscopic Club in Chicago (14).

Within this fertile milieu, the early semi-flexible gastroscope evolved such that in 1957, Basil Hirschowitz unveiled the utility of the fiber optic gastroscope at a meeting of the American Gastroscopic Society, and introduced the modern endoscopic age (18). Since that time there has been a rapid evolution in technology, including the introduction of the flexible gastroscope, tremendous improvements in optics and the mainstream use of videoendoscopic technology. Currently, existing technology continues to evolve to include endoscopic retrograde cholangiopancreatography (ERCP), the ultrathin and transnasal video endoscopes, and endoscopic ultrasound.

3.1.2 The Technical Performance of Diagnostic Esophagogastroduodenal (EGDE) endoscopy

More than 10 million gastrointestinal (GI) procedures are performed annually in the United States (15). In Canada, EGDE examinations of the upper digestive tract represents 51-65% of all GI endoscopic procedures performed in teaching hospitals (3). Diagnostic EGDE allows direct visualization of the esophagus, stomach and duodenum with the use of a standard 9.8 mm flexible gastroscope equipped with a standard video processor. The endoscope is inserted through the mouth of the patient who is positioned in the left lateral decubitus position, most commonly following local anesthesia of the posterior pharynx with topical xylocaine spray. The gastroscope is then passed either blindly or by direct visualization through the oropharynx to achieve intubation of the upper esophagus.

With the assistance of the video processor unit, computer LCD chip and a television screen, the physician can directly visualize the relevant anatomic landmarks including the esophagus, body of the stomach, pylorus, duodenal cap and the fundus of the stomach via retroflexion of the gastroscope. If necessary, biopsies can be taken with the use of forceps inserted through the therapeutic channel of the gastroscope. Therapeutic interventions such as injection therapy of bleeding lesions, removal of polyps, foreign object retrieval as well as thermal and mechanical coaptation of vascular malformations are also possible with the use of specialized instruments inserted through the therapeutic channel.

3.1.3 Common uses of the diagnostic gastroscopy

Recent large multicentre databases such as the Clinical Outcomes Research Initiative (CORI), introduced in 1995 in the United States have contributed to our knowledge of North American patterns of endoscopic use. The CORI initiative has revealed that the single-most common reason for EGDE is the evaluation of dyspepsia and/or abdominal pain (23.7%). Other indications include dysphagia (20%), symptoms of gastroesophageal reflux without dysphagia (17%), and suspected upper GI bleeding (16.3%) (16).

3.2 SEDATION

3.2.1 The role of sedation in the performance of endoscopy: topical and parenteral.

The standard use of sedation to facilitate the performance of EGDE was first established with the use of rigid and semirigid endoscopes. This trend has

continued despite the evolution of the technology, such that now in the United States, some authors have concluded that " it is the expectation of most patients in the United States that sedation and analgesia are provided for endoscopic procedures" (19). However, the perceived benefits of improved patient tolerance and satisfaction permitted by the provision of parenteral sedation must be weighed against the risk of adverse cardio-pulmonary events and the unit cost. It is estimated that sedation and related issues are responsible for up to 40% of total endoscopic cost (20). These costs encompass the unit cost and the loss of efficiency of the patient, as well as in the individual who must accompany the patient to a sedated procedure as an escort following discharge.

The goal of sedation and analgesia during the performance of EGDE is to increase patient tolerance of the procedure without compromising cardiopulmonary function and a patent airway. To achieve these goals, topical anesthetic throat spray and parenteral benzodiazepine and/or narcotic have been used, either in combination or independently. The main limitation to tolerance appears to be primarily pre-procedural anxiety and apprehension (12, 21, 22).

Hedenbro and Lindblom offered patients the choice of parenteral sedation or throat spray only. Parenteral sedation was requested by 34%, over half cited apprehension about the result of the test rather than anticipation of procedural discomfort as the reason for their request (12). Drossman et al. also surveyed patients regarding their pre-procedural apprehension. These authors note that sixty percent of patients had some pre-procedure concerns, including the final diagnosis and procedural discomfort. As well, they found that increased anxiety

was most related to female gender, younger age and first procedure (21). In comparison, Probert et al, found that most patients wished to be sedated regardless of whether or not they presented for their first procedure, or a repeat experience (22).

The choice of sedative regimen is varied, and a number of combinations have been examined. Commonly benzodiazepines (midazolam, diazepam) or narcotic agents (meperidine) are used parenterally for their anxiolytic and analgesic properties. Benzodiazepines induce relaxation, cooperation, and can introduce an anterograde amnestic response. When combined with a narcotic agent, significant respiratory depression can result (60). Doses are titrated based on the patient's age, co-morbidity and the complexity of the endoscopic intervention.

Analgesia is the reduction in pain or response to nociceptive stimuli induced by the use of medication, primarily opiates. Used in low doses, these opiates can reduce procedural discomfort without impairing consciousness. If used in higher doses, depression of the respiratory system is possible to a level comparable to that of a general anesthetic. The choice of agent, its use in combination or alone is left to the endoscopist. Often, the choice is dictated by the individual's experience as a trainee, and local practice patterns.

In 1991, Daneshmend reported in a survey that 90% of endoscopists in the UK favor the use of anxiolytics such as midazolam for the majority (75%) of their procedures while only 13% provided a narcotic agent for analgesia (23).

However, in a recently published retrospective study from the UK (61), a 54% decline in the use of parenteral sedation was noted for the performance of outpatient diagnostic gastroscopy, over a ten year period from 1989-1998 from a high of 72% (1990) to its lowest incidence of 32% (1998). This decline in sedation was most noticeable among females ($p<0.0001$) and in procedures performed by non-gastroenterologists. Furthermore, the decline in sedation rates was lower throughout the entire study period for patients endoscoped for the first time compared to those undergoing a repeat examination ($p<0.0001$). As well, the overall mean dose of midazolam used per case showed a statistically significant decrease from 5 mg to 2.9 mg ($p<0.0001$) over the time period examined. Despite this recent study showing a decline in sedation rates in the UK, trends regarding the use of sedation in diagnostic gastroscopy remain unknown for most other countries.

Generally, midazolam is used more frequently for sedation and analgesia than diazepam for both its superior amnestic properties and its reduced incidence of thrombophlebitis (25). Recent clinical trials by Mahajan et al. (26) and Van Houten et al. (27), have suggested that the emulsified form of diazepam (diazemuls) is effective for sedation, has less thrombophlebitic risk than conventional diazepam, and is significantly less costly when compared with midazolam.

Commonly in North America, the combination of anxiolytic and narcotic agents is used. This strategy has been shown in some clinical series to lead to improved patient tolerance. Diab et al., using a combination of meperidine and

midazolam noted decreased retching, improved intubation, tolerance, and procedural completion when compared to using an anxiolytic agent alone. (24)

However, the use of parenteral sedation must be individualized for each patient and the endoscopist's goals. The limiting factor to the use of parenteral opioid-based conscious sedation during endoscopic procedures remains excessive drowsiness and the loss of a patent airway and possible cardio-pulmonary compromise. As Zuccaro points out, the term "conscious sedation" dictates that patients receiving sedation and an analgesic should be able to respond purposefully to verbal stimuli (19). In fact, a patient responsive only to noxious tactile stimuli is deeply sedated; a situation warranting immediate resuscitative action.

However, the depth of sedation experienced by the patient is often difficult to predict. Ginsberg et al. (28) observed that the predicted appropriate dose administered for the performance of endoscopy was an overestimation in 21%. Furthermore, among senior citizens, the administered dose was often excessive. Bell et al. (29) and Scholer et al. (30) report similar findings in the performance of EGDE. Bell found that overestimation of the dose of conscious sedation was common, especially among patients greater than seventy years. Scholer noted that among the elderly, a rapid decline in the necessary dose of diazepam is required.

Despite the use of parenteral sedation, often the most uncomfortable segment of the endoscopic evaluation is the insertion of the endoscope into the

esophagus, the intubation. In a recent nationwide survey in the UK, it was noted that 63% of endoscopists facilitate intubation with the use of a pharyngeal anesthetic spray (21). However, the question of the efficacy of the additional use of topical anesthetic to decrease gagging, improve patient tolerance, and improve technical adequacy of the procedure remains controversial.

Among the eleven published controlled trials evaluating the effect of pharyngeal anesthesia, the reported benefit is mixed. Studies by Sparberg et al (31), Cantor et al. (32), Chuah et al. (33) and Daniel et al. (34), conclude that the use of pharyngeal anesthesia in combination with parenteral sedation was ineffective in improving patient tolerance. However, Sparberg (31) and Cantor (32) administered anesthetic in the form of gargles instead of sprays, and compared small groups of patients, thus making it difficult to draw any relevant conclusions. Furthermore, gargles whose use was widespread in the past have been largely replaced by anesthetic sprays, which have been shown to improve safety and ease of application (54). It is unclear from the existing literature if the efficacy of anesthetic sprays is superior to that of gargles.

Three studies by Gordon et al. (35), Jameson et al. (36) and Leitch et al. (38) have suggested an improvement in tolerance with the additional use of pharyngeal anaesthetic. The trial by Lachter et al. (39) concluded that pharyngeal anesthesia was of benefit to the endoscopist only during intubation among first-time examinees only, but was ineffective for increasing overall patient tolerance of the procedure (39). It is important to note that these studies all administered some form of intravenous sedation and some did not adjust for

previous gastroscopy experience or size of instrument used, which may have confounded the results of their analysis regarding efficacy of topical anesthetic.

It is well established that meperidine reduces gag reflex (55), thus in the Cantor or Sparberg studies any observable clinical difference noted by the use of topical pharyngeal anesthetic alone tended to be minimized. Davis et al. (41) in a single-blinded, prospective trial of 95 patients found no significant differences between diagnostic upper endoscopy with conscious sedation and topical anesthesia versus EGDE with no topical anesthesia with respect to ease of intubation, technical adequacy, procedure duration and doses of narcotic or benzodiazepine.

Only three of the published trials, Campo et al. (53) Hedenbro et al. (37) and Soma et al. (40), have evaluated the benefit of using topical pharyngeal anesthetic alone, without the concomitant use of conscious sedation. Soma attempted to identify whether the use of topical anesthetic spray alone could ease the discomfort of esophageal intubation.

This group concluded that the use of pharyngeal anesthesia did not significantly reduce patient discomfort with intubation (RR= 0.56, 95% CI: 0.31-1.01), but may be of use among those aged less than 40 (RR=0.21; 95% CI: 0.04-0.99) years in whom the RR of discomfort during intubation was twice that of those greater than 40 years (RR=2.22; 95% CI: 1.04-4.74), and among those undergoing an EGDE for the first time (RR= 0.20; 95% CI: 0.04-0.93). Furthermore, the use of anesthetic pretreatment had no impact on the

endoscopist's ability to intubate, nor did it improve the endoscopist's ability to perform a satisfactory endoscopy.

An important caveat to the Soma study is the methodology. The discomfort measures were obtained immediately following the procedure. Thus the outcome obtained may reflect the overall tolerance of the procedure rather than the actual discomfort experienced during intubation.

Campo et al. (53) showed an improvement in patient tolerance to an unsedated procedure in their randomized, double blind study examining the usefulness of pharyngeal anesthesia. Among 250 patients randomized, intubation and examination evaluated on visual analogue scales by patients were better tolerated (both $p=0.0001$) among those receiving active medication than those who received placebo. Furthermore, in contrast to the Soma study, endoscopists found intubation ($p=0.02$) and examination easier ($p=0.0001$) among those receiving topical anesthetic spray.

The Hedenbro study (37) used a similar protocol as the Campo study (53) in unsedated patients, and also showed an improvement in tolerance with the use of topical pharyngeal anesthetic. However, the collection of data regarding the outcome of interest involved the patient returning a questionnaire completed at home the next day. This strategy resulted in the exclusion of 15% of the patients who did not return their forms, and may have resulted in a selection bias and consequently, influenced their results.

Do patients exhibit a preference when it comes to the use of topical anesthetic? Randomized trials from Sweden (37) and Greece (42) revealed that no difference in throat discomfort was found between those who received anesthetic spray and those who did not. However, in the Swedish study a majority of patients preferred that any subsequent procedures be performed with the use of topical anaesthetic and in the Greek study a tendency towards improved tolerance was noted. Furthermore, in a prospective evaluation of over 2000 cases in the Middle East, it was found that the use of topical anesthetic spray permitted a safe, quick and well-tolerated procedure in the unsedated patient (11). Thus there exists a basis for the use of topical premedication (spray or gargle) based on mixed evidence from RCTs suggesting improved intubation and large prospective series of patient satisfaction and endoscopic tolerance.

3.2.2 Complications of gastroscopy and sedation

The performance of EGDE by an appropriately trained individual is quite safe. However, significant complications can occur as a result of instrumentation. These include the risks of bleeding, perforation and infection with a frequency of approximately 0.1% for upper endoscopy (56, 57). The risk for therapeutic procedures and emergency procedures can be considerably higher (58).

What are the potential risks associated with the use of anesthetic premedication? Complications from anaesthetic sprays or gargles are rare but are potentially lethal and include anaphylactic reactions (43), systemic toxicity

related to rapid anesthetic absorption causing toxic levels (44) and methemoglobinemia related to the use of benzocaine and lidocaine at high doses in children and predisposed persons (45-50). The residual effects of the numb oropharynx can rarely last greater than 45 minutes, impairing the cough reflex (51) and predisposing the patient to the risk of aspiration pneumonia. Consequently, patients are asked to not eat or drink for at least one hour following their procedure.

In comparison, the risks associated with parenteral sedation are much greater. Arrowsmith et al. (52) analyzed the data generated from over 21,011 endoscopic procedures performed with midazolam or diazepam pre-medication. They found that serious cardiopulmonary complications occurred in 5.4 of 1000 procedures, and death in 0.3 of 1000. Of interest was the observation that these complications were more likely to occur when a narcotic agent was used in combination with the benzodiazepine, or when emergency procedures were performed.

In Scandinavia, 52 deaths and 156 cardio-pulmonary arrests related to the use of parenteral conscious sedation were observed over a two-year period (23). The incidence of adverse events occurred with equal frequency when either midazolam or diazepam was used. Many authors have highlighted that the elderly patient (92, 92) or those with concomitant cardiovascular, pulmonary, renal, hepatic, metabolic, neurologic disorders or morbid obesity may be more susceptible to the risks of conscious sedation (5, 59).

3.2.3 *Practice guidelines for the care of the sedated patient undergoing gastroscopy*

Although rare, the perceived cardio-pulmonary risk to the patient has resulted in the development of practice guidelines for the administration of parenteral sedation and regarding the appropriate monitoring of the patient while they undergo a sedated procedure. In 1989, the American Society of Gastrointestinal Endoscopy (ASGE) published guidelines regarding sedation and monitoring of patients undergoing gastrointestinal endoscopic procedures (62). These highlighted the importance of clinical monitoring of sedated patients by a trained endoscopy assistant, and selective monitoring of physiologic parameters such as hemodynamics (heart rate, blood pressure and pulse oximetry) in high risk patients. (9)

Subsequently, the ASGE published a revision of these guidelines in 1995 (63). Once again, they emphasized that good patient care includes patient assessment prior to, during and after endoscopic procedures by appropriately trained staff and readily available intensive care and emergency backup. Appropriate monitoring should detect significant changes in hemodynamics, ventilatory status, cardiac electrical activity, clinical and neurologic status noted by comparison from the pre-procedure baseline measurements. These guidelines highlight the importance of routine pulse oximetry to follow the patient's oxygenation status and the use of a well-trained and vigilant assistant. Furthermore, these guidelines recommend that appropriate pharmacological

agents to reverse the effects of both benzodiazepine sedation (i.e. flumazenil) and opioid narcotics (i.e. naloxone) be readily available in every endoscopy unit.

The use of automated procedural monitoring (pulse oximeter, and EKG) is required in all high-risk patients, however the need for such intensive monitoring during routine endoscopy, has not been unequivocally demonstrated in controlled trials. (64) Bowton et al. (70) reported the clinically insignificant occurrence of transient oxygen desaturation to as low as 58% by pulse oximetry. Fassoulaki et al. (71) note that there is a similar incidence of transient desaturation among sedated and unsedated patients. However, other authors (74, 75, 76) have found a significant association between transient oxygen desaturation and the use of parenteral sedation. In comparison, the use of supplemental oxygen has been shown to reduce the magnitude and severity of oxygen desaturation when given during sedated endoscopic procedures (65, 66). However, the endoscopist must safeguard against the suppression of hypoxic drive and the resultant hypercapnea (67).

Perhaps the most important aspect of the sedated diagnostic EGDE is the necessity for further clinical monitoring of important physiologic parameters after the termination of the procedure. This observation period can be variable, and the length of follow-up is dictated by the perceived risk to the patient. However, it is imperative to monitor the patient following the sedated procedure, as the effects of hypoxia may persist long after the end of the procedure (68).

It is recommended that patients not be discharged from the unit until vital signs are stable and the patient has reached an "appropriate level of consciousness" (63). However, as the ASGE guidelines correctly point out, "despite the appearance of appropriate recovery, it is well recognized that patients may have a prolonged period of amnesia and/or impaired judgment and reflexes following intravenous medications administered to induce sedation" (63). To safeguard against this additional risk to the patient, it is recommended that all patients who receive parenteral sedation be accompanied home in the care of a competent companion, and they be advised not to operate heavy equipment or make legally binding agreements.

In addition to the guidelines offered by the ASGE, a special multi-disciplinary task force of the American Society of Anesthesiology (ASA) has recommended full monitoring for all patients undergoing gastroscopy with sedation (69). Some gastroenterologists, who have argued that they administer sedation in a way, which maintains protective reflexes, and therefore the rigidity of the ASA recommendations need not apply to the endoscopy suite, dispute the basis for such a strong recommendation. However as Zuccaro aptly points out, "sedation is a continuum, and prediction of an individual response to the administration of sedation and analgesia cannot always be predicted (19). It would seem prudent to adopt the most rigorous standards for monitoring, those based on the Accreditation Manual for Hospitals (AMH), which in the United States has stated that the standards of anesthesia care should apply whenever

sedation is administered which may reasonably result in the loss of protective reflexes.

In comparison to the American affinity for automated monitoring, the Canadian Consensus Conference on Endoscopy (8) suggests that the best monitors of sedation are the physician and a skilled assistant. However, standard clinical monitoring should include the pre, intra and post procedural measurement of basic hemodynamic parameters and ventilatory status. The authors of this guideline go on to state that: "oximetry is useful but does not replace clinical observation. " Nonetheless, it is noted that oxygen saturation is best detected by an oximeter, and can be useful for the detection of the rare occurrence when desaturation is associated with significant hypoxia, which when detected early can be appropriately managed. Thus the consensus statement concludes that the use of oximetry is " a rational recommendation in all cases of conscious sedation" (8).

Clearly the guiding principle for administration and monitoring of sedation in EGDE is the safety and comfort of the patient. Despite the fact that there exists no proof that routine monitoring of the average-risk, sedated patient reduces the incidence of cardio-pulmonary morbidity and mortality, these guidelines have been considered definitive and widely adopted from a medical-legal perspective (7). However, at this time there exist no consensus as to which patients should receive sedation prior to diagnostic gastroscopy.

3.3 Review of published RCTs

Possible advantages associated with performing diagnostic EGDE on unsedated subjects include a decreased incidence of cardio-pulmonary side-effects, a shorter examination time, decreased hospital costs, absence of anterograde amnesia and the immediate post-procedure ability to drive and work (88). However, there remains a paucity of methodologically rigorous placebo-controlled randomized controlled trials assessing the impact of sedation vs. no sedation in the performance of upper gastrointestinal endoscopy. Much of what is currently published examines small or selected groups of patients, lacks statistical power to differentiate between strategies and has not considered important clinical confounders and effect modifiers.

There have been only four published RCTs examining a policy of routine sedation vs. no sedation for the performance of diagnostic gastroscopy using a regular caliber (9.8 mm) endoscope. Both Fisher et al. (83), Christe et al. (92), Froehlich et al. (76) and Gombar et al. (73) have all randomized patients to sedation (benzodiazepine only) vs. no sedation in the performance of diagnostic gastroscopy. In these trials, a regular caliber (9.8mm) gastroscope was used to perform the diagnostic procedure, and topical pharyngeal anesthetic was used to ease the discomfort of intubation. However, the outcomes of interest were very different in these trials. Gombar et al. (73) chose to examine the effect of sedation on the physiologic parameters of oxygenation, and did not measure clinical outcomes of satisfaction, tolerance or willingness to repeat. He noted a

predictable and significant decline in oxygenation during the performance of sedated EGDE vs. non-sedated EGDE.

In the study by Christe et al., sixty-five geriatric patients, mean age 84 (SD: 7 years) were randomized in a double-blind manner to undergo diagnostic EGDE with either midazolam (benzodiazepine) or placebo (saline). Outcomes of patient self-reported tolerance, pain and breathing difficulties were assessed 2 and 24 hours post procedure using a categorical scale (1= very badly to 5= very well), as was willingness to repeat the examination under the same test conditions. The difficulty of the procedure assessed by the endoscopist (visual analog scale, 0= no problem to 10= impossible), standard cardiopulmonary and cognitive parameters (the Mini Mental Status Exam) were also assessed. These authors found that tolerance was improved in the sedated group (OR= 19.3; 95% CI: 2.2-170.4). Sedation was also associated with frequent circumstantial amnesia at 24 hours post-procedure (84% vs. 27%; $p<0.001$), more hypoxemia (44% vs. 18%; $p=0.033$) but had no major consequence on cognitive function. Christe et al. (92) used a rigorous placebo-controlled, double-blind study design, however, the generalizability of their results are limited due to the selection bias inherent in this study. Ninety-four patients had been approached to participate, with only 65 accepting to be randomized. Furthermore, their enrolment was limited to a geriatric population prone to polypharmacy and significant co-morbidity, which may have had a significant impact on the metabolism of benzodiazepine medications, thus altering the observed effect of exposure. Finally, their reduced sample size (n=65) contributed to very limited power and the consequent large

width of the confidence intervals generated. Further studies, with a similar design are necessary to draw definitive conclusions as to the safety and efficacy of sedated vs. unsedated EGDE in this selected population.

In 1995, Froehlich et al. (76) randomized 200 patients to one of four arms: (1) midazolam and lidocaine spray, (2) midazolam and placebo lidocaine, (3) placebo midazolam and lidocaine spray, and (4) placebo midazolam and placebo lidocaine. Measured outcomes included patient tolerance (visual analog scale 0= excellent to 100= unbearable), pre-procedural anxiety (visual analog scale measuring "fear of the procedure" where 0= "not at all" and 100= "enormous") and willingness to repeat. The endoscopists rated the difficulty of the procedure (0= easy to 100= extremely difficult) and the extent of patient collaboration (0= excellent to 100= extremely limited), as well as four specific symptoms (vomiting, cough, belching and "defense reactions"), which were arithmetically factored into a technical adequacy score. The use of sedation with pharyngeal anesthetic resulted in improved patient tolerance (23 points vs. 36 points on VAS; 95% CI: 15-32) and willingness to repeat (96% vs. 74%; $p<0.001$). However, it had little bearing on the endoscopists' rating of procedural difficulty ($p=0.89$).

Froehlich's study uses four randomization arms in a limited sample of patients. In his comparison of outcomes between treatment allocation groups, the total sample size was only 49 to 51 patients per treatment group, yet the power of the subgroup analysis is sufficient enough to detect a clinical difference with reasonably narrow 95% confidence intervals. However, it is difficult to interpret the impact of sedation vs. no sedation on the technical adequacy of the

procedure, as the "defense mechanisms" which were factored into the outcome were poorly described and defined in the methodology. Nor does the author indicate which percentage of the total population eligible to participate, agreed to participate. Knowledge of the acceptance rate for participation would further strengthen the generalizability of the results generated.

Fisher et al., measured clinical outcomes including the patient-centered outcomes of self-reported comfort and willingness to repeat the procedure under similar test conditions. As well, the endoscopist was asked to rate not only the ease of intubation, but also the overall difficulty of the procedure. For all clinical outcomes, a numerical scale of 1-5 was used, where 1 represented the most favorable and 5 the least favorable response. Their results suggested that the endoscopists rated both intubation and the procedure as slightly easier in the *non-sedated group* (p=non-significant), however, sedated patients were significantly more comfortable than non-sedated patients (p=<0.001). Despite this difference in patient self-reported comfort, there was no statistical difference between groups when asked if they would be willing to repeat their procedure under similar test conditions.

Fisher's results, though intriguing, must be interpreted with caution. Examination of the methods reveals the presence of significant absence of blinding, leading to possible observation bias. Of 282 patients initially approached for randomization, only 100 agreed to participate. Although 100 patients were randomized, randomization did not occur in a blinded fashion, thus significantly compromising the validity of the clinical outcomes measured. Both

the endoscopist and the patient were cognizant of the treatment arm. Prior to their procedure, patients were advised by mail with regard to their randomization arm. Furthermore, patients were given the opportunity to withdraw from the study if they wished. As well, the possibility for recall bias exists in the data collection of post-procedural patient satisfaction. Self-reported satisfaction with comfort was reported via the administration of a questionnaire, which they were asked to complete within 24 hours of their EGDE. However, the author's do not reveal the percent of returned questionnaires, nor do they acknowledge the amnestic properties of midazolam, which may impair a patient's ability to recall their comfort during the test procedure. Finally, among this self-selected group of patients, there were very few females (77 men & 23 women). Thus the authors were unlikely to detect any significant gender differences among the sedated vs. non-sedated groups, nor are their results generalizable outside of the clinical context of "self-selected, probably non-anxious and predominantly male group (in which) the principal findings have been demonstrated" (83).

Fisher's study highlights the need for a methodologically sound, rigorous, double blind RCT comparing the efficacy of sedation vs. no sedation in the performance of diagnostic EGDE. Many questions remain unanswered regarding the feasibility, tolerability and generalizability of unsedated diagnostic EGDE in a North American population. This is of particular interest with the recent availability of "ultrathin" endoscopies, which have an outer diameter of 6.0mm vs. the 9.8 mm diameter of the standard instrument. With their introduction there has been a renewed interest in the performance of unsedated

gastroscopy in the United States (84, 86, 89-91). A complete appraisal of the "ultrathin" endoscopy literature is beyond the scope of the current review. However, the socioeconomic impact of this technology is potentially significant.

Prior to the widespread diffusion of ultrathin endoscopes as the "only" technology suitable for unsedated gastroscopy, a rigorous investigation of unsedated conventional gastroscopy merits re-examination, to attempt to answer the many questions that remain regarding feasibility, tolerability and generalizability of unsedated diagnostic EGDE, given the state of the existing published literature.

4. THE RANDOMIZED CONTROLLED TRIAL

4.1 Study Justification:

There has been widespread adoption of the routine sedated EGDE in North America despite inadequate evaluation of alternative strategies. Can diagnostic EGDE be performed comfortably and in a technically sound fashion without the routine use of intravenous sedation? The data presented in this project is an attempt to quantify the efficacy of EGDE with sedation vs. no sedation in an adult ambulatory Canadian population. This is important as the indiscriminate use of routine sedation potentially increases the risk of significant cardiorespiratory complications and costs of the procedure.

Once the efficacy of both strategies (sedation vs. no sedation) has been quantified, it might be possible to assess differences in efficacy among certain subgroups of patients. In a prospective observational study by Abraham et al.

(75), it was suggested that adult ambulatory patients older than 55 years of age and with decreased pharyngeal sensitivity could best tolerate an unsedated diagnostic EGDE. A large scale randomized controlled trial is necessary to explore the possibility that there exists a subset of patients in whom an unsedated EGDE can be performed in a successful manner.

4.2.1 Study Hypotheses:

1- At the group level, sedation will have a positive effect on patient satisfaction and willingness to repeat the procedure, however, the technical adequacy of the procedure will not differ between the two groups.

2- Performance of diagnostic gastroscopy without sedation may be more efficacious in selected patients—those aged greater than 55 years and those with decreased pharyngeal sensation. In all other subgroups, the performance of sedated diagnostic gastroscopy is expected to be more efficacious than a non-sedated procedure.

4.2.2 Study Objectives:

1. To quantify the efficacy of a policy of routine sedation vs. no sedation in the performance of upper gastrointestinal endoscopy in the adult ambulatory care population.

2. To explore in a preliminary fashion, the subgroup of patients (those greater than age 55 and with decreased pharyngeal sensitivity) in whom an

unsedated gastroscopy may be performed comfortably and in a technically adequate fashion.

3. To assess the appropriateness of continued enrollment of the study, a planned interim analysis will be conducted once >50% of enrollment has been achieved.

4. To determine the effectiveness component of a subsequent comparative study of cost-efficacy of two approaches: routine administration of sedation as compared to (intent of) no sedation among patients undergoing a diagnostic gastroscopy.

4.3 METHODS

4.3.1 Study design:

This study is a double blind, placebo controlled randomized trial initiated in 1999 at two participating sites of the McGill University Health Centre (Montreal General and Royal Victoria Hospitals). Patients were randomized patients to undergo EGDE with standard parenteral sedation vs. placebo. The primary base from which this study population is drawn is a racially and ethnically diverse outpatient population from a large metropolitan Canadian city (over 4,500,000 in population). Patients presented to one of two participating hospitals of the McGill University Health Centre (the Royal Victoria Hospital and the Montreal General Hospital). The overall number of EGDE performed by the primary co-investigators at this university centre totals about 500-600/year of which approximately 80% are done on outpatients for diagnostic purposes.

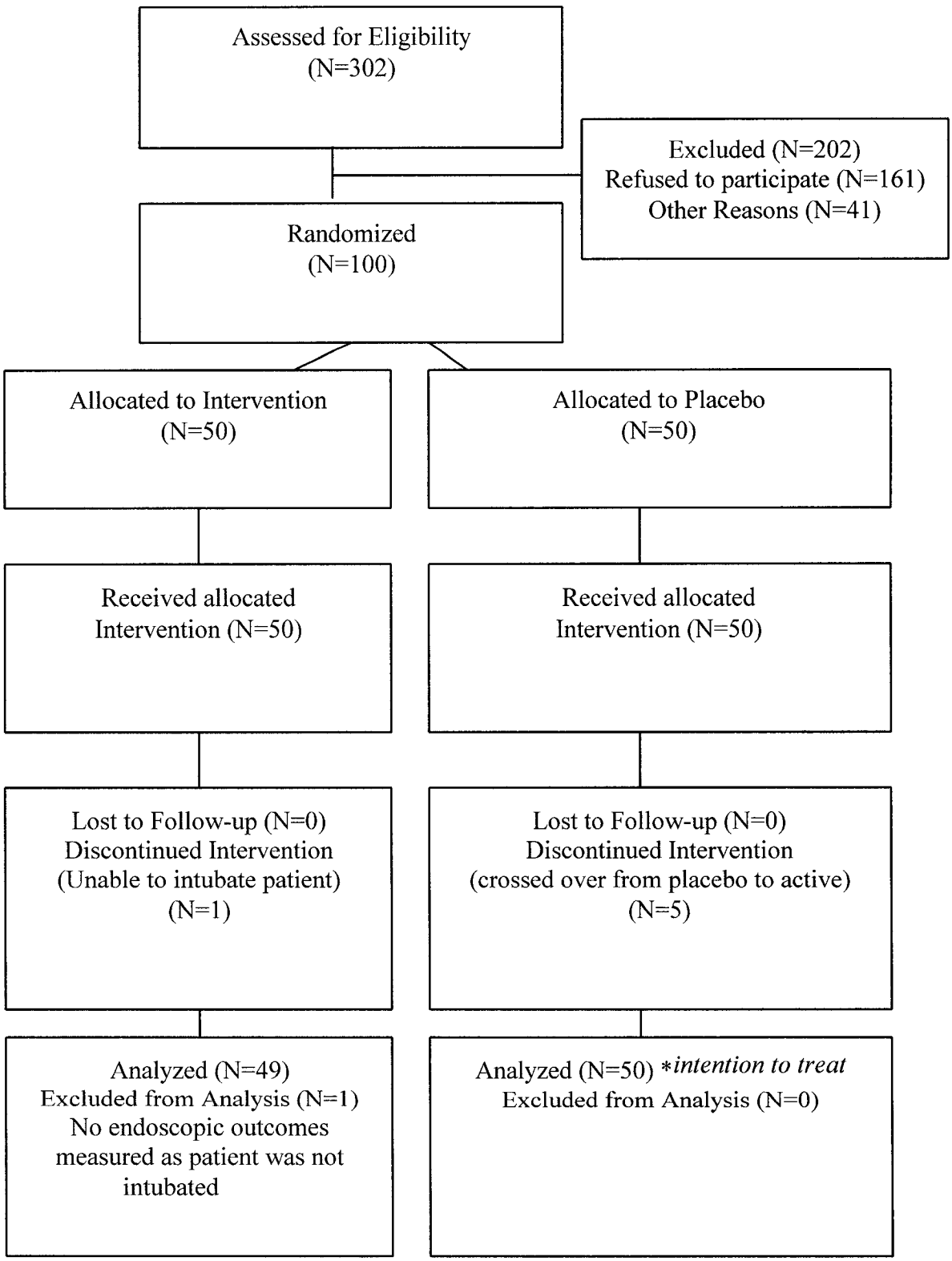
From the start of the enrolment period (June 1999) potential patients were identified from the outpatient endoscopy list, and those scheduled for a diagnostic EGDE were approached by the research coordinators, in a consecutive fashion and invited to participate in the trial. Written institutional consent, approved by the Ethics Review Committee, was obtained in all cases. Patients were centrally randomized in a blinded fashion, and clinical outcomes were assessed in a systematic manner, respecting blinding as described below.

4.3.2 Study population

This study was initiated in June of 1999, with the first patient recruited in the first week of June. All consenting ambulatory adult patients (>16 years of age) deemed fit and scheduled for a diagnostic EGDE (i.e. without a planned therapeutic component) with one of the participating endoscopists, at one of the two participating sites were eligible to participate.

A study log was completed for the first three months of recruitment in 1999, which revealed that in the first three months of enrolment (ending August 1999), 302 patients were invited to participate in the trial. One hundred patients accepted to participate and 202 patients declined. Of the 202 patients who refused to participate, 161 consented to complete the same demographic questionnaires as those randomized. The remaining 41 patients declined all participation (including questionnaires), however, demographic data and the reasons for refusal were documented on all. See patient flow chart as described in Figure 1.

Figure 1. Diagram of Subject Flow Through the Phases of Randomization (1st 3 Months of Enrollment)



We were thus able to determine if there existed any relevant clinical differences among those patients who agreed to participate in our trial, and those who refused. Thus allowing us to assess the overall generalizability of our results as they pertain to the patients who accept participation in our RCT. These data have been previously presented in abstract form by Abraham et al. (107), and are summarized in the forthcoming results section.

4.3.2.1 Inclusion criteria

Potential subjects were required to fulfill the following inclusion criteria: patients of legal age able to consent, no other significant cardio-respiratory or medical co-morbidities precluding their participation nor any known documented allergy to the anaesthetic spray, lidocaine, no anticipated need for antibiotic coverage or therapeutic endoscopic intervention.

4.3.2.2 Exclusion criteria

Exclusion criteria included: low baseline oxygen saturation, significant pre-existing respiratory co-morbidity, emergency procedures, patients with an American Society of Anesthesiologist physical status classification (ASA score) greater than 4 (suggesting severe systemic disease) (115), patients with a documented drug dependence or a documented oro-pharyngeal swallowing disorder.

4.3.3. Study outcomes

The **main outcome** is "successful endoscopy", a measure of clinical efficacy. "Successful endoscopy" was defined as a composite score of patient satisfaction with the procedure as well as quality of the examination

(technical adequacy) as assessed by the operator. These were determined by the administration of standardized Likert scales as previously published by Walmsley et al. (104). **Secondary outcomes** included patient satisfaction alone, doctor's satisfaction alone, technical adequacy of the procedure and patient's willingness to repeat the procedure under similar test conditions.

Measurement of the primary outcome: Immediately following the EGDE, the endoscopist scored the technical adequacy of the examination. Each anatomic area (esophagus, stomach, up to the second stage of the duodenum and retroflexion in the body of the stomach) that was adequately viewed, received a score of 1 if adequately viewed versus 0 if inadequately viewed. Therefore a total perfect score out of 4/4 was assigned if all four anatomic areas of the examination were well visualized. Similarly, at the completion of their examination prior to being told the results of their procedure, patients were asked to rate their level of satisfaction from 1= acceptable to 5= unacceptable. The composite outcome of "successful endoscopy" was both technically adequate (i.e. 4/4 as rated by the endoscopist) and comfortable for the patient (1-2/5 satisfaction as rated by the patient).

Measurement of the secondary outcomes: Standardized Likert scales were used to measure the secondary outcomes of satisfaction. Patients were asked to rate their satisfaction with their comfort following the recovery period and prior to receiving their endoscopy results. They rated their procedures as 1= acceptable to 5= unacceptable. The physician was also asked to rate his/her satisfaction with the procedure, immediately following extubation, as 1=

unacceptable to 5= acceptable. Willingness to repeat was assessed by the administration of a telephone verbal rating scale (yes/no) 24 hours following the procedure. Finally, the technical adequacy of the procedure as assessed objectively by the endoscopist, as previously described under the section "measurement of primary outcome".

4.3.4 Randomization

Patients were randomized in blocks of 20 by a computer generated randomization list produced centrally by an independent biostatistician. In the field, the principal investigators, the subjects, the study statistician, and the research nurses involved with the recruitment of the patient were all blinded to randomization group.

Once the patient had been screened by the research coordinator and informed consent obtained, that patient received a study number. An endoscopy nurse, that was participating in the performance of the EGDE and *not* participating in the measurement of study outcomes, randomized the patient to intervention or placebo based on the assigned study number, and allocation remained concealed to the investigators/patient and research coordinator by means of a system using sequentially numbered, opaque, sealed envelopes.

4.3.5 Study interventions

Primary Intervention: Concealment of allocation was respected by the preparation of the study medications by the endoscopy nurse outside the

procedure room, and by the labeling of the syringes of medication or placebo as "D" (meperidine or placebo) or "V" (midazolam or placebo). Both the active medication and normal saline have a transparent appearance in the syringe, thus limiting the possibility of unblinding by the endoscopist who administered the drugs (see section "blinding/unblinding procedure" below).

In the intervention group, all patients were administered titrated intravenous doses of meperidine and/or midazolam according to the patient's tolerance and clinical status. The dose administered was determined by the individual endoscopist and recorded for each patient. In the control group, all patients received an equivalent titrated dose of normal saline placebo. Only the study medications were administered in all cases. In both groups, if the subsequent gastroscopy was unsuccessful due to patient intolerance, patients were given titrated doses of sedation in an open label fashion, without breaking the blinding. The doses required of active substance were noted. These patients were designated as "cross-overs".

Co-interventions:

Assessment of Pharyngeal Sensitivity and Anaesthesia: In all patients, prior to intubation, increased pharyngeal sensitivity was clinically assessed in a fashion that most accurately replicated "real-life" clinical practice. During the administration of the topical pharyngeal spray, the physician noted the presence or absence of a strong gag reflex (defined *a priori* as the constriction of

the pharynx in response to the stimulus where the posterior pharynx could not be visualized prior to the first application of anaesthetic spray).

In keeping with our routine clinical practice, during the application of the anaesthetic spray, the applicator tip did not directly touch pharyngeal tissue. With each atomized application of anaesthetic, the endoscopist observed the patient's pharynx for evidence of constriction as defined above. Consistent with the local practice, all patients received a titrated dose of lidocaine spray (on average, 12 ml per metered dose) for pharyngeal anesthesia, until the physician felt the patient's oropharynx was adequately anaesthetized. The total metered dose of administered lidocaine was recorded and was examined as a potential confounder. Furthermore, to ensure that the individual variability in the operator's use of topical anaesthetic was not a confounding variable, subsequent multivariate models generated included each operator as a covariate.

Endoscopic procedure (EGDE): Each patient underwent a standard EGDE performed by a member of the attending staff or an appropriately supervised GI fellow. A standard 9.8 mm gastroscope was the instrument of choice in most cases (Olympus America Inc., Melville NY, USA), however, <2% of patients underwent EGDE with a therapeutic or paediatric gastroscope. An examination was considered technically adequate if each anatomic landmark of the upper gastrointestinal tract (oesophagus, stomach, up to second stage of the duodenum and retroflexion in the body of the stomach) was adequately viewed. An endoscopy nurse and research assistant were present for each examination.

The administration of verbal analgesia/encouragement: The degree to which the patient would likely receive verbal encouragement and coaching throughout their test EGDE was noted by using as proxy a record of the operator and endoscopy nurse. The encouragement of patients during any test procedure is common, and excessive encouragement may contribute to patient outcomes such as satisfaction alone and willingness to repeat. Thus it will be considered as a potential confounder and effect modifier of the exposure outcome relationship.

4.3.6 Possible confounders and effect modifiers

Possible confounders that were recorded included: demographic characteristics (gender, age, level of education, cultural background), life style (smoking, alcohol use), and selected variables measured by the administration of a specially developed questionnaire (Questionnaire 1). This questionnaire assessed a number of covariates including: previous experience with endoscopy, expectations of endoscopy, and pharyngeal sensitivity of the patient as observed by the endoscopist during the application of topical anaesthetic spray (as defined above) (10, 12, 78).

Other possible confounders and effect modifiers noted were the level of experience of the operator (staff vs. resident), the administration of verbal analgesia (we used as proxy a record of the operator and nurse involved with the endoscopy), the indication for the EGDE, any noted difficulty with the procedure, the diameter of the scope (standard 9.8 mm vs. pediatric or therapeutic size), the

dose of xylocaine administered, and prior history of gastroscopy with sedation (or without sedation).

As part of the initial assessment, a validated anxiety questionnaire was administered to all patients (79) in questionnaire 1. The Hospital Anxiety and Depression Scale (79) is a brief, validated self-assessment scale developed to detect depression and anxiety in the setting of hospital outpatient clinics. It features fourteen items, of which seven relate to the outpatient assessment of the psychiatric manifestations of anxiety disorders in the internal medicine population. Scores of 7 or less are associated with non-cases, scores of 8-10 with doubtful cases and scores greater than 11 with definite cases of anxious patients. This scale has undergone appropriate psychometric evaluation, and has previously been used in the outpatient endoscopy setting (78) to determine if the patient exhibited clinically significant anxiety.

4.3.7 Data Collection Procedure

Data collection began once the patient signed the informed consent form to participate in the study. The study nurse who remained blinded to the subject's study allocation carried out the pre-procedural assessment (questionnaire 1: described above) and post-procedural assessment (questionnaire 2: items related to procedure time, technical adequacy score, doctor and patient satisfaction scores, doses of medications used, complications or adverse events and 24 hour post-EGDE assessment of willingness to repeat) with the use of specially designed data abstraction booklets.

Following the return of the patient from the recovery room, patient outcomes of satisfaction alone were assessed at three time intervals-- prior to being told the results of their examination while still blinded to study allocation, prior to discharge from the endoscopy suite (once allocation group and procedure results were known) and 24 hours after the procedure. (This final assessment interval was measured as it was thought to provide the most accurate reflection of patient satisfaction among those who may have suffered the amnestic effects of sedation).

However, for the primary composite outcome of "successful endoscopy" and the secondary outcome of "patient satisfaction alone", the first assessment of patient satisfaction was chosen as it was felt to reflect the least biased outcome, which avoided possible confounding by reassurance or anxiety evoked by the added information of test results. The patient conditions for outcome assessment will thus be similar to before the procedure except for the patient's appreciation of the discomfort solely attributable to the gastroscopy.

The research coordinator collected data regarding the technical adequacy of the procedure and the physician's satisfaction alone with the EGDE immediately following extubation of the patient, as well as the physician's impression of whether or not the patient had received sedation. The patient's willingness to repeat the EGDE under similar test conditions was collected by standardized telephone interview 24 hours following the procedure. Crossovers and complications were also recorded.

4.3.8 *Blinding/Unblinding Procedure*

If the patient was randomized to the intervention group, meperidine 50 mg (1 cc of 50 mg/cc solution) and midazolam 2 mg (2 cc of a 1 mg/cc solution) were each drawn into separate 3cc syringes as is standard of care in both the endoscopy units of the Montreal General and Royal Victoria hospitals. The syringes were labeled D (for Demerol, the brand name of meperidine) and V (for Versed, the brand name of midazolam) respectively. If the patient was randomized to the control group, equivalent quantities of saline were drawn up in two syringes labeled D and V respectively. All medications were prepared outside the endoscopy suite, by an endoscopy nurse who was aware of the patient's treatment allocation, but was not involved with the patient assessments in the study. Such that all staff participating in the endoscopic examination or patient assessments remained blinded, and concealment of allocation could be assured.

The endoscopy nurse who prepared the study medication, was available to provide urgent unblinding of the study medications if the patient's clinical status warranted unblinding. The participating study nurse, who remained blinded to treatment allocation, noted the procedural characteristics, and assessed the patient outcomes. Due to the rapidity by which active medication can sometimes exert its sedative effect in patients, it is biologically implausible to completely ensure complete blinding of the endoscopist, when patients are randomized to active vs. placebo medications. Therefore, we asked all endoscopists to record their impression of whether or not the patient was

sedated following the procedure, prior to unblinding. This would permit examination of the effect of possible unblinding at the level of the endoscopist on the clinical outcomes.

4.3.9 Sample size and power estimate

The sample size calculation used data from available literature in a comparable population with regards to patient satisfaction and adequacy of the examination with or without sedation. It is important to note that small differences in efficacy were anticipated between both groups. Based on earlier studies, we anticipated satisfaction rates of 75-80% in non-sedated, and 90-95% in sedated patients (76-78). We used this conservative estimate on purpose to overpower our calculation and thus, to permit a clinically relevant observational subgroup analysis.

Our sample size calculation is also based on the assumption that similar results were anticipated for the percentage of "successful endoscopy", the main outcome of interest, in the two groups. To date, no prior studies have combined both the patient self-reported satisfaction with their level of comfort *and* the technical adequacy of the procedure as the primary clinical outcome of interest. Previous authors have patient tolerance (76, 92) and patient self-reported comfort alone (83) as the primary outcome of their RCTs, and have either failed to, or limited their comments with regard to technical adequacy of the procedure.

However, we believe that a truly successful EGDE is one that is *both* comfortable for the patient and technically adequate. Furthermore, we hypothesized that technical adequacy would not be affected by sedation status, thus the estimates of patient self-reported comfort or tolerance alone were used to generate sample size and power calculations.

The sample size was calculated to have sufficient power to detect the smallest possible difference in main outcome between both groups, i.e a 10% difference. Using sample size estimation methods for the comparison of two proportions we determined that a total of 575 patients would be required to detect a difference of 10%, with a Type I error of 0.05 and a power of 90%. The current sample size of 360 will allow us to detect a difference as small as 13% with the same Type I error and power.

This sample size (N=360) will allow us to detect an effect size of 0.78 of sedation on the secondary outcomes. Thus there is adequate patient numbers by most subgroups, to identify clinically interesting trends in a preliminary fashion. These noted trends in the interim analysis, can then be compared to those obtained by subgroup when the trial reaches completion of its total enrolment (N=575).

4.3.10 Statistical Analysis

The data were analyzed using an "intention-to-treat" approach i.e. subjects were retained in the study group to which they were first randomized even if they subsequently did not comply with the assigned treatment. All

statistical analysis was carried out using the Statistical Analysis System (version 8.0; SAS Institute Inc, Carey, NC). Preliminary analyses included descriptive statistics (mean and standard deviation for continuous variables and frequencies for categorical variables) for all measurements for the intervention and control groups separately. To assess the success of randomization, the distribution of baseline variables in the two groups were compared descriptively. Significant correlations between variables of interest were identified with the use of 2X2 tables for discrete variables, and Pearson Correlation Coefficients for continuous variables.

Variables that were not equally distributed, using clinical judgment, were noted as possible confounders (i.e. an important third co-variate which is associated with the exposure and is a risk factor for the outcome). When the Mantel-Haenszel OR for estimates varied by greater than ten percent from the crude estimate, a confounding variable was thought to exist, and included as a separate co-variate in multivariate logistic regression.

The crude effect of sedation on each outcome was measured using the absolute difference (and 95% confidence interval) comparing treatment and control groups. Crude odds ratios (and 95% confidence intervals) were also used to determine the effect of sedation and of each covariate on the outcome measures. Potential effect modifiers (i.e. interaction) of the crude relationship for any covariate was considered when a measure of association (i.e. OR) differed among strata, such that the crude estimate fell between the stratified estimates and the Breslow-Day test of homogeneity was <0.02.

Separate logistic regression models were fit to evaluate the effect of sedation on each outcome after adjusting for the effect of other covariates. Age, pharyngeal sensitivity, gender and anxiety were regarded as potentially necessary covariates due to their prior reported associations with both the use of sedation and the performance of successful endoscopy (10, 12, 53, 78), and were thus included in all models. Other covariates included those that appeared to be confounders or effect modifiers based on preliminary analyses.

Using Pearson's correlation coefficient for continuous variables and 2X2 tables for categorical variables, the possible correlation between covariates was assessed. Linearity for continuous and ordinal exposures was checked using logit plots. Logarithmic and quadratic transformations were evaluated in case of evidence of non-linearity.

Candidate models were compared using BIC criteria (Bayesian Information Criterion) (116), which adjusts for both the number of covariates and the sample size. Lower values of this criterion indicate a better fitting model. The models were compared to examine the impact of adding covariates on the magnitude and precision of the main association using the likelihood-ratio test. The goodness of fit of candidate models was assessed using the Hosmer-Lemeshow test. To adjust for the fact that this is an interim analysis we used the methods of Jennison and Turnbull (80) to determine an appropriate critical value (2.004) for the 95% confidence interval of the odds ratios.

4.3.11 Ethical considerations:

This study received certification of ethical acceptability for research involving human subjects from the McGill Faculty of Medicine Institutional Review Board (Appendix 5). Furthermore, informed written consent, as judged ethical by each institutional review board, was obtained from all patients prior to entry into the study protocol. The complications of gastroscopy (EGDE) were disclosed including cardio-respiratory complication, medication reactions (including allergy), bleeding, perforation, and phlebitis. The risk of driving, operating heavy machinery or completing sophisticated cognitive tasks following sedation is routinely discussed with the patients following the procedure.

4.4 RESULTS

4.4.1 *Patient Population*

The subject flow diagram (Figure 1; see page 36) provides information about the progress of patients throughout the first three months of the trial. From this initial time period, when a complete study log was kept, we were able to assess any differences in characteristics or baseline variables between the group of patients who accept participation in our trial, and those who refuse. Thus allowing us to assess the overall generalizability of our results as they pertain to the patients who accept participation in our RCT.

Comparison of baseline variables and covariates among those patients who agreed to participate and those who refused randomization revealed no significant differences in most categories including pharyngeal sensitivity, gender, anxiety level, past medical history, procedural indication and

pain tolerance. However, three patient characteristics were strongly predictive of refusal of enrollment. Those patients that had received treatment for an anxiety disorder, used regular pain analgesics, or had previously undergone EGDE were most likely to refuse enrollment in the trial. None of these patient characteristics had previously been identified by our group as an independent predictor of the need for sedation or the comfort of the gastroscopy (75). These covariates were considered in the subsequent multivariate analysis.

At the end of ten months (June 1999-March 2000), only 360 patients had been randomized. If we extrapolate from the information obtained from the first three months of recruitment, our acceptance rate was only 33%. It was anticipated that to achieve our total sample size of 575 patients, an additional 633 patients would need to be screened. Thus, for the purposes of this thesis, an interim analysis was completed on this population, which represents 63% of the total anticipated sample size.

In the cohort of 360 patients, 51% were female, the mean age was 54.2 yrs (SD 16.3 yrs). The majority was of Caucasian race (83%), non-smokers (84%), and 60% had obtained a university education. Among the cohort group, 10% of patients were regularly using prescription sedatives, 10% were regularly using prescription analgesics, and 9.5% reported regular use of prescription anxiolytics. One hundred and seventy-one patients (47.5%) had previously undergone EGDE, and 73% had a positive expectation of their upcoming procedure. Overall, 43% reported general anxiety and 24.5% were noted to have pharyngeal sensitivity at the time of their procedure. The most common indication

for the diagnostic EGDE was "dyspepsia" (62%) and biopsies were taken in 79.5% of cases. Attending GI staff performed the majority of the procedures (91%) and a standard 9.8 mm gastroscope was used in 95% of cases. Table 1 shows the distribution of baseline patient and procedural characteristics according to randomization group. Characteristics between both randomized groups were clinically similar, suggesting success of our randomization process.

4.4.2 *Correlation between variables*

A number of the anxiety related variables (ex: use of prescription sedatives, treatment for an anxiety disorder, use of prescription anxiolytics and the presence of anxiety) were highly correlated. Thus the presence of anxiety was chosen to be a surrogate marker of these other anxiety related variables.

All three measures of patient satisfaction were highly correlated with the majority of patients rating their comfort during EGDE as acceptable (80-85%). Therefore, the first measured outcome of patient satisfaction (prior to being told the results of the examination, while still blinded to exposure status) was chosen for both the patient satisfaction component of the composite primary outcome, as well as for the subgroup analysis of patient satisfaction alone. This was chosen as it was felt to be the least biased measurement of patient self-reported comfort.

4.4.3 *Ensuring Blinding*

The MD (endoscopist's) impression of the patient's sedation status was highly correlated ($p<0.0001$) to randomization group (sedation vs. placebo);

yet, only 80% of endoscopists were accurate in their assessment of the sedation status of the patient.

4.4.4 Effect of Sedation

Effect on primary outcome—"successful endoscopy": Among all 360 patients, 61.4% of procedures (221 EGDE procedures) were considered "successful" as defined by technical adequacy and patient self-reported satisfaction with comfort. The use of sedation resulted in a higher percentage of successful EGDE procedures (83% of sedated procedures vs. 39% of unsedated procedures: Risk difference= 0.46; 95% CI: 0.37 to 0.55). Overall, 80.9% of patients randomized to placebo were able to complete their procedure without sedation. The remaining 34 patients required sedation to complete their procedures.

Effect on patient satisfaction alone: Sixty-one percent of patients expressed satisfaction with their level of comfort during their EGDE. When stratified by sedation status, 83% of sedated patients were satisfied vs. 39% unsedated; Risk difference= 0.46; 95% CI: 0.37-0.55.

Effect on doctor satisfaction alone: Eighty-one percent of endoscopists were satisfied with the patient's level of comfort during the EGDE overall (92% sedated vs. 71% unsedated; Risk difference = 0.36; 95% CI: 0.25-0.47).

Effect on patient willingness to repeat: Seventy-two percent of patients were willing to repeat their EGDE under similar test procedures.

However, patients were more willing to repeat their procedure if they had been sedated (85% sedated vs. 59% unsedated; risk difference = 0.32 with 95% CI: 0.21-0.43).

Effect on technical adequacy: The overall technical adequacy rate of the EGDE procedure as rated objectively by the endoscopist (by adequately visualizing all four regions of the upper gastrointestinal tract—esophagus, body of stomach, duodenal bulb and fundus of stomach) was 98%. There was no difference in technical adequacy between exposure groups (97% unsedated vs. 99% sedated; risk difference= 0.22 with 95% CI: -0.11-0.56).

4.4.5 Clinical predictors of "successful endoscopy"

Clinical predictors of a "successful endoscopy" are outlined in Table 2. The use of sedation (OR= 7.52; 95%CI: 4.6-12.3/ Risk Difference 0.46; 95% CI: 0.36-0.55), and if the patient had positive expectations of their procedure (OR 2.1; 95%CI: 1.3-3.3/ Risk Difference 0.15; 95% CI: 0.05-0.24) appeared to be important predictors. Other possible predictors included anxiety (OR= 0.68; 95%CI 0.44-1.05/ Risk Difference 0.1; 95% CI: -0.20-0.01), pharyngeal sensitivity (OR=0.66; 95%CI: 0.40-1.08 / Risk Difference 0.08; 95% CI: -0.17-0.02) and age greater than 55 years (OR=1.39; 95%CI; 0.91-2.13 / Risk Difference 0.04; 95% CI: -0.05-0.14). However, the latter predictors did not reach statistical significance despite being of clinical interest.

There were five main indications for the diagnostic EGDE, of these only the indication "heartburn" was significant (OR 0.64; 95% CI: 0.42-0.99 / Risk Difference 0.11; 95% CI: 0.004-0.21). As the main indications were thought to be clinically those of symptoms of heartburn/indigestion (i.e. dyspepsia) vs. those of potential structural disorders (ulcer-like pain, vomiting or difficulty swallowing), a composite, dichotomous indication variable measuring dyspepsia (yes/no) was created. The composite measure of dyspepsia approached statistical significance (OR= 0.68; 95% CI: 0.44-1.05 / Risk Difference 0.09; 95% CI: -0.19-0.009).

Among the education variables those patients with less than a high school education appeared to differ from those who had obtained at least a high school education. For this reason, education was dichotomized by those who graduated from high school vs. those who did not.

4.4.6 Model Selection Process for "Successful Endoscopy"

Multivariate analysis identified exposure to sedation as the most significant independent predictor of a "successful endoscopy" (Appendix 1). The BIC for the model with intervention group alone as a covariate was 416.5 (Model #1 in Appendix 1). All multivariate models included the variables sedation, age greater than 55 years, the presence of pharyngeal sensitivity or anxiety, and positive expectations of the procedure based on *a priori* substantive knowledge of their association with sedation and the outcome, the hypothesis of the study and the results of the bivariate analysis (Table 2).

With the addition of these variables to the crude model, the BIC improved to 400.3 and the odds ratio of a successful endoscopy increased to 8.6 (95% CI: 5.0-14.6) (Model #8 in Appendix 1), suggesting that with the additional covariates, the fit of the model to our data improved. Replacing the dichotomized covariate "age" as a continuous measure, in this model did not appreciably change the BIC value (Model #9 in Appendix 1). The inclusion of educational status, gender, indication of dyspepsia, endoscopist and prior EGDE to this model did not contribute to a further improvement in the BIC criteria.

4.4.7 Subgroup Analysis/Effect Modification on "Successful Endoscopy"

Table 3 summarizes the stratified analysis examining possible effect modification. Potential effect modifiers of the crude relationship between sedation and the performance of a successful endoscopy (the crude estimate [OR= 7.5] falls between the stratified estimates and the Breslow-Day test is <0.2) were examined. They included smoking status, the endoscopist (procedure performed by attending staff), positive expectations of the procedure, prior history of EGDE, pharyngeal sensitivity and the presence of anxiety. When compared to the crude model (only the covariate of randomization to sedation vs. no sedation), age>55 was not a significant effect modifier. Other age cut-offs were examined to note whether or not they exerted an important biologic effect modifying the exposure-outcome relationship. The cut-off of age>65 was not an important effect modifier, however, the cut-off of age>75 did show an interesting

trend approaching statistical significance (Table 3). However, this cut-off was excluded in the subsequent multivariate models due to the paucity of subjects in the strata age>75 (N=41).

Multivariate models were constructed considering each of these potential effect modifiers on the base model (sedation, age>55, pharyngeal sensitivity, anxious, positive expectations) (See Appendix 1). Modeling suggested that sedation was the most important predictor of a successful endoscopy, however, other patient characteristics did contribute to improved or diminished odds of a successful endoscopy. The results of adjusting for the effect modifiers are as follows (Table 3):

- **Subgroup "Age >55":** Older patients, i.e those greater than 55 years had a greater likelihood of a successful endoscopy (OR = 10.7; 95% CI: 4.8-24.2) than those patients younger than age 55 (OR= 7.1; 95% CI: 3.5-14.5).
- **Subgroup "Smoking Status":** Non-smokers had a greater likelihood of successful endoscopy (OR= 10.2; 95% CI: 5.7-18.4) when compared to smokers (OR= 3.2; 95% CI: 0.9-11.0).
- **Subgroup "Pharyngeal Sensitivity":** Patients without pharyngeal sensitivity (OR= 11.7; 95% CI: 6.2-22.3) have higher odds of successful endoscopy than those with increased pharyngeal sensitivity (OR= 3.8; 95% CI: 1.5-9.9). However, the interaction between pharyngeal sensitivity and randomization group is not considered statistically significant in our sample due to the limited number of subjects in some strata (i.e.

randomized to sedation with pharyngeal sensitivity and having an unsuccessful EGDE where N=10). However, note is made of the high correlation between pharyngeal sensitivity and smoking status (r=0.77; p=0.02).

- **Subgroup "Staff Endoscopist":** There was a greater likelihood of a successful endoscopy if the EGDE was performed by a staff endoscopist (OR= 9.6; 95% CI: 5.5-17.0) compared to those EGDE procedures performed by residents (OR= 2.9; 95% CI: 0.55-15.1).
- **Subgroup "Prior History of EGDE":** Patients without a prior history of EGDE had greater odds of a successful endoscopy (OR=13.3; 95% CI: 6.3-28.20) when compared to those with a prior history of EGDE experience (OR=5.4; 95% CI: 2.5-11.5).
- **Subgroup "Anxious Patient":** The effect of sedation was less important in anxious patients (OR= 5.9; 95% CI: 2.8-12.5) than non-anxious patients (OR= 12.0; 95% CI: 5.6-25.2).
- **Subgroup "Positive Expectations:** Patients with negative expectations of their procedure had greater odds of a successful endoscopy (OR=10.6; 95% CI: 4.0-28.1) vs. those with positive expectations of their procedure (OR= 7.8; 95% CI: 4.2-14.7).
- **Subgroup "Gender":** A trend toward a greater likelihood of successful endoscopy among male patients (OR=9.8; 95% CI: 4.9-19.5) was suggested when compared to female patients (OR=5.6; 95% CI: 2.8-11.3). However, the interaction between gender and randomization group is not

considered statistically or clinically significant due to the limited number of subjects in some strata (i.e. male patients randomized to sedation and having an unsuccessful EGDE where N=15).

- **Subgroup" patients >55 years with no pharyngeal sensitivity":** Those patients who were among our subgroup of interest were 13.8 times more likely to experience a successful endoscopy when sedated (OR=13.8; 95% CI: 5.8-32.9) when compared to those who were less than 55 years with pharyngeal sensitivity (OR=3.4; 95% CI: 1.2-9.6), with a risk difference of 0.49 (95% CI: 0.35-0.63) and a power to detect a difference of 98.9%. However, among this subset of patient, those patients randomized to placebo have a greater likelihood of successful endoscopy when compared to other subsets randomized to placebo (45% successful vs. 39% among the unstratified placebo population).

A likelihood ratio test (LRT) was applied to all models with candidate effect modifiers (Appendix 1), to determine if the addition of the interaction term resulted in a significant improvement. Only the addition of the interaction terms including age>55, smoking status and prior EGDE, resulted in a significant p-value (<0.05), suggesting that there is sufficient evidence to reject the null hypothesis of no effect of the interaction term on the odds ratio associated with sedation. However, note is made of lack of power in some subgroups (i.e those *with* pharyngeal sensitivity (N=84); 79% power), to examine statistical or clinical significance during the model selection process (Appendix 1).

When goodness-of-fit (GOF) diagnostics using the Hosmer-Lemeshow Chi-Square probability (where the H_0 = model is a perfect fit) were applied to these candidate models, only the model containing the interaction term for age>55 (#13 GOF p=0.83) yielded a superior fit of the model than #8, the base model which excluded the interaction terms (GOF p= 0.64). Therefore, although there were seven important modifiers of the relationship between sedation and successful endoscopy, the best fitting model includes only the effect modifier of age>55.

4.4.8 Secondary outcomes

4.4.8.1 Willingness to Repeat

72 % of patients were willing to repeat their procedure under similar test conditions (sedated: 84.9% & unsedated: 59.4%; Risk difference=0.32; 95% CI: 0.21-0.43). There were three potential predictors of willingness to repeat: female gender (OR 0.43; 95% CI: 0.26-0.69) randomization to sedation (OR 3.84; 95% CI: 2.31-6.39) and dyspepsia as the indication for the procedure (OR 0.45; 95% CI: 0.27-0.76) (Table 4). Age greater than 55 years, male gender and smoking status were possible effect modifiers of the association between sedation and willingness to repeat.

After model creation based on predictors and potential confounders, two candidate base models, (# 2, in Appendix 2) (sedation, scope time) and (#3 in Appendix 2) (sedation, scope time, gender, dyspepsia), were chosen based on the BIC. The inclusion of interaction terms for possible effect modifiers and

additional was done separately for both base models. The application of a likelihood ratio test to both models including interaction of sedation with age, gender of smoking did not sufficiently improve the base models, and thus they were excluded. Although goodness of fit diagnostics (GOF) between both base models: #2 (sedation, scope time) and #3 (sedation, scope time, female gender, dyspepsia) were similar, model #2 (sedation, scope time) was chosen as the optimal model as it was the most parsimonious and made the most clinical sense.

4.4.8.2 Patient Satisfaction Alone

Immediately following their procedure, and just prior to being told the results of their study, 61.9 % of patients reported satisfaction with their level of comfort during their test procedure (sedated: 83% & non-sedated: 39.3%; Risk difference=0.46; 95% CI: 0.37-0.55). The strongest predictor of patient satisfaction alone was randomization to sedation vs. no sedation (OR 9.53; 95% CI: 4.55-19.96) (Table 5). However, other strong predictors included positive expectations of the procedure (OR 2.04; 95% CI: 1.16-3.58) and gender (OR 0.51; 95% CI: 0.29-0.88). Stratified analysis revealed two possible effect modifiers of the crude relationship, pharyngeal sensitivity (OR=4.5; 95% CI: 1.4-14.8) and procedure performed by attending staff (OR=9.84; 95% CI: 4.5-21.5).

The three best models (Appendix 3) based on the aforementioned criteria were: sedation, gender and positive expectations of the procedure (BIC=304.20); sedation, gender, positive expectations, pharyngeal sensitivity and

the interaction between sedation and pharyngeal sensitivity (BIC=304.53); and sedation and positive expectations alone (BIC304.58). In choosing between these three candidate models with similar SC values, it is noted that the precision (i.e. 95% CI of OR for "sedation") of the third model is poor. The LRT examining the impact of the interaction term suggests that the presence of pharyngeal sensitivity is an important effect modifier of the relationship (LRT= 11.27 with 2 d.f; p= 0.0025-0.005). Thus, the model which includes the variables sedation, gender, positive expectations and the effect modifier pharyngeal sensitivity is the optimal model for estimation of the relationship between sedation and patient satisfaction alone.

4.4.6.2 Doctor Satisfaction Alone

81.7% of endoscopists rated the test procedure as "acceptable" on a Likert Scale designed to assess their overall impression of the EGDE (sedated= 92.3% & non-sedated= 70.8%: Risk difference=0.36; 95% CI: 0.25-0.47). The procedure's rating by the endoscopist as "acceptable" was not influenced by the technical adequacy of the procedure. As when the endoscopist's satisfaction of the procedure was stratified by technical adequacy, similar proportions were noted (sedated 92.7% vs. 72.3% unsedated: Risk difference=0.34; 95% CI: 0.23-0.46). There were only two potential predictors of this outcome, randomization to sedation (OR 4.95; 95% CI: 2.63-9.33) and shorter time to perform the procedure (OR 0.51; 95% CI: 0.29-0.88) (Table 6).

Stratified analysis highlighted the presence of two other important clinical modifiers of this relationship pharyngeal sensitivity and gender.

The model selection process identified two models based on their clinical relevance, their similar BIC criteria (appendix 4) and the performance of the LRT. Model #2 (sedation, pharyngeal sensitivity) yielded the smallest BIC (318.22), but this was only marginally superior to model #3 (sedation, pharyngeal sensitivity, scope time: BIC 319.97). GOF diagnostics supported the choice of model 2 (sedation, pharyngeal sensitivity; GOF= 0.55) as the best model when compared to the GOF of model 3 (GOF=0.17).

4.5 Adverse Events

Among the 360 participating patients there were no intra or immediate post-procedural complications. There were no cases of cardio-respiratory complications among the cohort. No patients required admission following their procedure, nor did any patients report adverse events for the first 24 hours of follow-up. One patient (0.003%) did complain of a sore throat that persisted for one week following his procedure. This patient had received placebo and had rated his procedure as satisfactory immediately post procedure.

4.6 DISCUSSION

4.6.1 Discussion of Study Results:

Despite the fact that diagnostic gastroscopy can be performed safely and in a technically adequate fashion without sedation, there is still tremendous

worldwide variation in the standards of practice. Waye noted the prevalent use of sedation in North America and South America (72%) as compared to Europe (56%) and Asia (44%) (81). Especially in the United States, there is still a reluctance to eliminate the use of pharmacological agents in selected endoscopic situations.

This hesitation may be a reflection of the concern that the endoscopist's reputation is primarily based on the comfort and tolerance experienced by the patient during the procedure (82). However, there arguably exists sufficient evidence to suggest that the unsedated diagnostic gastroscopy is not only technically feasible, but is also acceptable to many patients and caregivers alike. Previous work by Fisher et al. (83), Froehlich et al. (4, 76), Al-Aktrachi (11), Hedenbro et al. (12), Sorbi et al. (84), Rey (85) and the recent work of Mulcahy (61) help support the notion that the unsedated outpatient diagnostic gastroscopy is well tolerated, safe, feasible and widely accepted by patients as evidenced by a high willingness to repeat the procedure under similar conditions. Yet it remained unclear as to the feasibility of unsedated diagnostic gastroscopy in the Canadian North American population.

The present trial represents the first fully published study comparing the efficacy of sedated vs. unsedated diagnostic gastroscopy in a North American population, performed in a Canadian healthcare setting. Overall, only 61.4% (sedated: 83% & unsedated: 39%; Risk Difference=0.46; 95% CI: 0.37-0.55) of procedures were considered "successful" as defined by technical adequacy and patient self-reported satisfaction with comfort. This proportion is

similar to that of patient satisfaction alone with their self-reported comfort (61.9%). When asked to rate their level of comfort in their treatment allocation group, of the 61.9% of patients who reported high satisfaction with their comfort, 83% of satisfied patients had been randomized to sedation.

Our results suggest that although most patients (80.9%) randomized to placebo were able to complete their procedure without sedation, only 39.3% of non-sedated patients were truly satisfied with their comfort during their test procedure. Consequently, only 59.4% of non-sedated of patients were willing to repeat their procedure under similar test conditions compared to 84.9% among those who were sedated.

Of interest was the similar proportion of technically adequate EGDE procedures amongst both randomized groups. The high technical adequacy rate of 98% suggests that the *quality of the examination* is not compromised by the absence of sedation. However, when endoscopists were asked to rate their satisfaction with the procedure, only 81.7% of procedures were considered acceptable (92.3% of the sedated vs. 70.8% of the unsedated). The technical adequacy of the procedure did not appear to influence the endoscopists' satisfaction with EGDE. With similar proportions for endoscopist satisfaction noted when the procedures were stratified by technical adequacy.

The lower overall rate of endoscopist satisfaction with the procedure despite excellent technical adequacy may reflect the perceived discomfort experienced by the non-sedated group. It is important to note, however, the discrepancy in perceived comfort during the EGDE as noted by the physician

(81.7% overall) vs. the patient (61.9% overall). This highlights the importance of using the *patient's self-reported rating of comfort* in the composite score (i.e. "successful endoscopy") as opposed to a physician's surrogate assessment of patient tolerance.

Among all clinical variables examined, randomization to sedation was the strongest single clinical predictor of the primary outcome ("successful endoscopy") (OR 7.52) and the secondary outcomes of patient satisfaction alone (OR 9.53), willingness to repeat (OR 3.84) and doctor satisfaction alone (OR 4.95) (Tables 2, 4). Previous authors have also highlighted the importance of sedation in the performance of diagnostic gastroscopy (76, 83, 92).

However, our analysis suggests that other features in addition to the provision of parenteral sedation are important in assuring a successful endoscopy, patient and physician satisfaction and willingness to repeat. Indeed, pharyngeal sensitivity, (female) gender and pre-procedural anxiety all had a negative impact on the clinical outcomes, whereas age>55 and positive expectations of the forthcoming procedure were associated with improved outcomes.

Consistent with our previous clinical observations (75), age and pharyngeal sensitivity (as demonstrated by the presence of a marked gag reflex during the topical administration of oropharyngeal anaesthetic) were again important clinical variables useful in predicting a successful endoscopy, patient satisfaction and willingness to repeat. The presence of pharyngeal sensitivity was an important clinical predictor of successful endoscopy, such that its presence

decreased the odds of a successful endoscopy (OR= 0.66; 95% CI: 0.44-1.08). However, it did not prove to be an important effect modifier of the primary outcome (i.e. an important statistical independent subgroup) due to the limited number of subjects in some strata (Ex: those randomized to sedation who had pharyngeal sensitivity and had *unsuccessful* EGDE), but was included as a potential predictor in the final model selection process for "successful endoscopy" based on *a priori* clinical knowledge. Nonetheless, pharyngeal sensitivity was an important effect modifier of both patient and doctor satisfaction alone.

This is in keeping with previous results (37, 53, 86), including those of Pereira et al. (13), who confirmed that anxious patients who had their procedure performed with the assistance of topical anaesthesia found their endoscopy just as comfortable as those patients who were sedated, and would undergo a repeat procedure under similar conditions. Unlike our trial, Pereira (13) did not examine the impact of previous gastroscopy experience and patient expectation in his study.

The potential benefit derived from the use of topical anaesthetic preparations prior to gastroscopy is controversial. Some authors suggest that topical anesthesia is beneficial in easing the discomfort of intubation thus improving patient tolerance (37, 53), while others contend that there exists no clinical difference between placebo and topical anesthetic spray with regard to ease of intubation, cough or gag response (39, 41, 94). However, it is important to note that the use of topical anesthetic spray was not the primary exposure of

interest in our study. Rather, we wished to study the effects of sedation vs. no sedation on the performance of diagnostic EGDE.

Accordingly, all patients received pharyngeal anesthetic in a standardized fashion as previously described, thus eliminating this covariate as a potential confounding variable. As well, among our cohort there were no documented adverse events of systemic toxicity such as anaphylactic shock, methemoglobinemia or hypersensitivity (43, 44, 95-97) related to the administration of topical pharyngeal anesthetic.

The importance of advancing age (age >55) in predicting a successful endoscopy was also confirmed by previous work done by Abraham et al (75) and Froehlich et al (76). In the Abraham study, 40% of 30 year olds with increased pharyngeal sensitivity could undergo a successful unsedated endoscopy as compared to 59% of similar patients aged 65. This rate increased further to 70% if the older patients had decreased pharyngeal sensitivity (75). Froehlich et al (76) in a double-blind randomized controlled trial also found that tolerance of unsedated gastroscopy increased in patients older than 40 years of age.

The reason for this improved tolerance with advancing age is unclear, but has been reported by several investigators including Zaman (89), Dumortier (91) and Tan (99). Perhaps the improved ability of the elderly to tolerate unsedated gastroscopy is caused by differences in the strengths of the agents used for pharyngeal anesthesia, or may simply reflect a physiologic difference in pharyngeal sensory function (100). Previous authors have noted

the absence of gag reflex in elderly subjects which may reflect an age-dependent decline in the integrity of the efferent pathway of the reflex, which occurs as an isolated abnormality of the neurological examination in the absence of disease patterns in elderly without overt functional impairment (106).

In the present study, age greater than 55 was not an important effect modifier on the performance of successful endoscopy, however, with advancing age (i.e.>75 years) a statistical trend toward significance was noted, however, we lacked a sufficient number of randomized patients in this strata of interest (age>75 years: N=41).

This suggests that perhaps the examination of an older subset of patients would be more useful in determining the relationship between decreased pharyngeal sensitivity and the performance of successful *unsedated* EGDE. Our study population was too young to thoroughly examine this clinical question, as the age cut-off of 55 years marks the approximate mean of our population (54.2 years). In the future, this data could be used to simulate an ROC curve to estimate an appropriate age threshold cut-off and enrollment could be stratified accordingly in a subsequent study.

One cannot underscore the importance of a patient's personality on their attitudes toward conscious sedation in the performance of diagnostic gastroscopy. A patient's apprehension about an endoscopic procedure is universal. Individual factors such as personality, prior gastroscopic experience and the presence of a high level of anxiety will influence the performance of a successful endoscopy, and the subsequent satisfaction and willingness to repeat

of the patient (101). A number of investigators have attempted to measure the psychological factors associated with endoscopic procedures and their impact on clinical outcomes of satisfaction and tolerance (10, 12, 21, 23, 77,78).

Consistent with our current results, were the findings of Campo (102) and Froehlich (76) that pre-endoscopic anxiety score had a significant impact on tolerance of the procedure. Indeed, the presence of pre-procedural anxiety decreased the odds of a successful endoscopy (OR=0.68; 95% CI: 0.44-1.05). Martin et al (98), Hoare et al (10), Mulcahy et al (88) and Drossman et al (21) have all shown that a higher pre-examination anxiety score, female gender and younger age are associated with decreased tolerance of unsedated endoscopy. Arguably the beneficial effect of low dose benzodiazepine administration on patient satisfaction is not due to the amnestic response, but due to the anxiolysis provided by such agents.

These authors (10, 21, 98) have also suggested that a previous unpleasant endoscopic experience may also contribute to decreased tolerance and patient satisfaction. In our study, 47.5% of those randomized had undergone a previous gastroscopy with or without sedation. Based on their prior experience, stratified analysis (Table 3) revealed that those patients who had undergone a previous procedure were five times as likely to have a successful endoscopy as compared to those who had no prior endoscopic experience, who had an OR of 11.38 for successful endoscopy. Do these patients have different expectations of endoscopy? Do they know their diagnosis as a result of previous endoscopic investigation? Would these patients have asked for sedation if they

had not been randomized? These questions are impossible to answer within the context of this study, but merit future consideration.

Similar to the findings of Froehlich (76), our multivariate analysis, failed to identify prior endoscopic experience as an important effect modifier of the relationship between exposure and successful endoscopy. It is interesting to note the consistency of our findings with Froehlich (76), the only other investigator to have investigated previous endoscopic experience in a double blind, randomized trial. However, the clinical impact of previous endoscopic experience only highlights the complexity of inter-individual psychological factors, which have an impact on the tolerance and acceptance of unsedated gastroscopy.

Our results imply that young apprehensive women are less likely to repeat their procedure if unsedated (OR=0.43; 95% CI: 0.26-0.69) and are less likely to be satisfied with their level of comfort during an unsedated procedure (OR= 0.51; 95% CI: 0.29-0.88). This improved tolerance of unsedated gastroscopy among men is consistent with the results of Dumortier (91), Tan (99), Froehlich (76), Hedenbro (12), Mulcahy (88) and Hoare (10). Others, including Fisher (83), Walmsley (104) and Zaman (103) dispute this gender-specific finding. The conflicting results regarding gender differences among authors may be explained by the heterogeneity in the procedural indications, the size of the gastroscope used (standard 9.8 mm versus ultrathin 5.3 mm), the route of intubation (per oral versus transnasal), study design (cohort study vs.

randomized controlled trial), gender variability in anxiety level, cultural differences between countries and patient expectations.

Campo and Brullet (102) suggested in 1999, that another reason for gender differences in tolerance maybe explained by a greater number of examinations performed for so called "functional disorders". These disorders of visceral sensitivity (i.e. dyspepsia) are common, however, females are most likely to seek medical attention for their symptoms. Accordingly, a gender bias can be introduced in the data. Our randomization process prevented such a bias from being introduced.

Two hundred and twenty-two patients randomized in the study had symptoms of dyspepsia. Of these patients 47% were male and 53% were female, suggesting no gender differential and limiting the possibility of a gender bias due to procedural indication. It is interesting to note that those patients who underwent EGDE for dyspepsia were less likely to repeat their test procedure under similar test conditions (OR 0.45; 95% CI: 0.27-0.76). As the measurement of "willingness to repeat" was assessed 24 hours post-procedure (once sedation status and the results of the intervention were known), it remains unclear whether this reluctance is a result of the therapeutic benefit generated by "a negative endoscopy" (21), or a reflection of the type of anxious patient personality who seeks medical investigation for a functional disorder.

The influence of smoking on successful endoscopy is intriguing but lacks clinical confirmation by other authors using rigorous methodology. Our study suggested that smoking status was an important effect modifier of the

association of the exposure (sedation vs. no sedation) and the primary outcome of successful endoscopy. Nineteen percent of our study population smoked (56 patients). If the patient was indeed a smoker, the likelihood of successful endoscopy decreased from OR=9.02 among non-smokers, to an OR=2.55. This difference in odds ratios suggests the identification of an important clinical variable strongly associated with the outcome, but not associated with sedation (exposure) status. Furthermore, note was made of the made of the high correlation between pharyngeal sensitivity and smoking status (r=0.77; p=0.02). This raises the possibility that the use of the interaction term for smoking in the model selection process for successful endoscopy, may possibly act as a surrogate for pharyngeal sensitivity. Is it biologically plausible that, with the constant pharyngeal irritation secondary to cigarette smoke, there is a subsequent alteration in pharyngeal sensitivity?

The physiologic explanation for improved tolerance among non-smokers remains unclear. No good randomized controlled trials have been conducted examining the clinical impact of smoking status on the performance of sedated or non-sedated diagnostic gastroscopy. Campo et al (102) consecutively enrolled 509 patients to undergo diagnostic EGDE after the administration of only a topical anaesthetic. His univariate analysis suggested that smoking status was a significant predictor of poor tolerance amongst patients who had no prior endoscopic experience (poor tolerance: 40% smokers versus 26% non-smokers; p=0.02) and those with prior EGDE experience (poor tolerance: 39% smokers versus 20% non-smokers; p=0.002).

Gelly et al (105) also consecutively enrolled a cohort of patients to participate in an open-label cohort trial evaluating the acceptability of a new topical pharyngeal anaesthetic. Tolerance of unsedated endoscopy was assessed using visual analog scales. Among thirty-seven patients at two sites, there were nine smokers. They suggested that there was a strong trend for smokers to be less tolerant of unsedated endoscopy than non-smokers. However, these pilot data must be interpreted with caution. No standardized delivery of topical anesthetic was used, nor was the sample size large enough to detect significant differences among competing confounding variables. Furthermore, the trial was not randomized nor double-blinded. Their findings can be considered hypothesis generating at best.

Both Froehlich (76) and Christe (92) considered the impact of smoking on patient tolerance and satisfaction with unsedated endoscopy. Smoking was not found to be an important predictor in either study. However, in the study by Christe et al (92) among the sixty-five patients randomized only eight were smokers, this small number may have resulted in an inability to detect a clinical difference between both sedated and unsedated individuals.

The population randomized in Froehlich's study (76) was more homogeneous with 23 smokers and 28 non-smokers. However, they failed to comment on the clinical implications of smoking status in their predictive models. Thus, at this time, the impact of smoking on unsedated endoscopy remains unclear. One might speculate that the increased oropharyngeal irritation induced by regular smoking, may increase the patient's discomfort with the intubation

phase of an unsedated endoscopy. Clinical studies are required to further characterize the relationship between smoking status and tolerance/satisfaction with comfort.

4.6.2 *Discussion of Adverse Events and Safety:*

There were no significant peri-endoscopic complications encountered in our study. The lack of a complication may be partially due to the fact that therapeutic and emergent cases were excluded. Furthermore, patients were selected from an ambulatory care setting, thus less likely to have significant cardio-pulmonary co-morbidity which may have put them at increased risk of complications related to sedation. As well, patients were monitored as recommended by the guidelines set forth by the Canadian Association of Gastroenterology (8), and transient hypoxemic episodes considered clinically irrelevant by the endoscopist, were not documented by study protocol.

However, it is important to note that our study was not powered to assess the incidence of cardio-respiratory complications, as this was not the principal outcome of interest. As the incidence of cardio-respiratory complications is rare, 5.4 in 1000 (52), a sample of greater than 900 patients would be necessary to detect a clinically significant complication rate of 0.5-1% with 80% power. At our current sample size of 360, we have only 11.2% power to comment on the occurrence of adverse cardio-respiratory events associated with the use of sedation vs. no sedation in the performance of EGDE.

4.6.3 *Strengths and Limitations of Study Design:*

This study has some important strengths worth noting. First, it was a large randomized double-blind controlled trial, in which 97% of enrolled patients were successfully contacted for follow-up. As such it contributes to the small world literature comparing sedated vs. unsedated diagnostic gastroscopy. Randomization was performed to address the risk of potential unknown confounders. The success of our randomization process is clearly demonstrated by the homogeneity of patient characteristics outlined in Table 1. Of note is the equal distribution of male and female subjects, allowing us to accurately assess gender differences with regard to test performance and patient preference for sedation.

All potential patients presenting for ambulatory endoscopy were approached to participate and there were very few exclusion criteria. Independent observers were responsible for data collection (i.e. health-care professionals not directly responsible for the medical care of the patient), and patients were assured of complete confidentiality in the data abstraction booklets and documentation of 24-hour follow-up.

As well, we were careful to ensure that patients themselves rated their satisfaction with their level of comfort (i.e. tolerance) during the procedure. Tolerance was evaluated by the endoscopists (11, 23) rather than the patient themselves in early studies. This may have contributed to inaccurate conclusions being drawn with regard to patient tolerance and the feasibility of unsedated EGDE.

The post-procedure patient centered outcomes were assessed following recovery from sedation, prior to disclosure of randomization arm and EGDE results. With this approach, we avoided possible confounding by reassurance or anxiety evoked by the added information of the test results or sedation status. Thus, the patient conditions for outcome assessment were similar to those prior to the procedure except for the patient's appreciation of the discomfort solely attributable to the gastroscopy. Almost all patients (97%) were contacted for follow-up within 24 hours of their procedure, minimizing the risk of recall bias.

Several limitations of this study are noteworthy. Although we hoped to ensure that the study nurse assessing the clinical outcomes, the patient and the participating endoscopists were blinded to the randomization group, we were unable to guarantee blinding of the endoscopist to randomization group in all cases. Despite the fact that the active and placebo preparations were identical in appearance, it is biologically plausible that an experienced endoscopist can predict whether or not a patient has received active medication by their reaction to invasive endoscopy.

To determine if this potential breach in our blinding process was a confounding covariate, we recorded the endoscopist's impression of the patient's sedation status following the procedure (prior to unblinding) in 77.2% of cases. There was 80% correlation between the endoscopist's impression of sedation status and the actual randomization group. This suggests that experienced endoscopists can often accurately predict the randomization group. When the

study population was stratified by the endoscopist's impression of randomization group, the lack of physician blinding *did not* prove to be a confounding variable (Mantel-Haenszel OR=6.41; 95% CI: 3.4-12.05), but should be examined as a potential effect modifier in a larger sample of patients (to ensure adequate power).

Secondly, our study was conducted at a tertiary university center. Future work in this area should be conducted in multiple locations, including both tertiary and community based hospitals. At this time, the results of our study of efficacy have yet to be validated in a real-life community hospital setting (i.e. a study of effectiveness).

The quantification of patient satisfaction with their comfort during the endoscopic experience remains difficult. Without the existence of a gold-standard validated endoscopic satisfaction scale, it remains difficult to accurately assess patient and endoscopist satisfaction. As well, it remains impossible to compare and standardize the results published by different investigators. The American Society of Gastrointestinal Endoscopy (ASGE) Governing Board recently endorsed a modified version of the Group Health Association of America-8 (GHAA-9) patient satisfaction survey (108) to attempt to quantify quality indicators in endoscopy.

Yacavone et al (109) in a recently published article in Gastrointestinal Endoscopy, attempted to use this GHAA-9 scale to assess satisfaction among endoscopy patients, as well as to identify and prioritize the elements inherent in the prediction of patient satisfaction. After administering

their modification of this scale to 559 patients with prior endoscopic experience, they found that the technical adequacy of the endoscopist was the most important predictor of patient satisfaction. However, the second most important predictor was the patient's perceived satisfaction with their comfort during the procedure. Unfortunately, an accurate assessment of patient satisfaction with self-perceived comfort was not addressed by any of the 15 items included in their modified GHAA-9 scale.

Thus, at this time, there exists no rigorously tested and validated questionnaire that addresses post-endoscopic satisfaction of the patient or the endoscopist. Nor does there exist an accepted biometric tool capable of accurately assessing the performance of a successful endoscopy (one that is both technically adequate in the opinion of the operator, and comfortable in the opinion of the patient). Previous authors have used either a visual analog scale (12, 41, 76, 77, 102, 111) or a variation of the Likert scale (24, 83, 84, 89, 92, 112). We chose to use a constructed variable based on a 5 point Likert Scale modified from that used by Walmsley et al (104), to obtain our primary outcome of "successful endoscopy" and the secondary outcomes of patient satisfaction and doctor's satisfaction alone (endoscopist). However, the risk of using a five-point Likert Scale is the possibility of ceiling and floor effects (109), limiting the discriminant ability of the measurement tool.

As well, we were limited in our ability to assess pharyngeal sensitivity of the patient. Previous investigators have used the presence and/or strength of the gag reflex as a surrogate marker of pharyngeal sensitivity (10, 12,

31-34, 37, 39, 40, 53, 78). Yet, most have failed to provide a definition of the presence of absence of an abnormal gag reflex, in order to standardize the assessment of pharyngeal sensitivity.

Our study methodology did attempt to define the presence of a strong gag reflex (see section 4.3.5), however, our definition is limited by the subjective judgment of each endoscopist assessing the severity of pharyngeal sensitivity. We did not attempt to assess inter-observer reliability of the assessment of gag reflex. Furthermore, interpretation of these results would be easier if the frequency of gag reflex and pharyngeal sensation in healthy subjects were known (106). Thus, we may have underestimated the true incidence of pharyngeal sensitivity in our population, due to the subjective nature of the estimation technique. However, our strategy to reproduce "real-life clinical practice" in our assessment of pharyngeal sensitivity is clinically sensible in the absence of an established validated method.

We lacked sufficient power in many subgroups of interest (i.e. those with pharyngeal sensitivity; elderly patients) to conclusively explore the impact of some patient characteristics of clinical interest on the primary outcome. In our analysis, we did not have enough patients in all strata (i.e. patients randomized to active medication with pharyngeal sensitivity and had unsuccessful EGDE; patients >75 years of age), to comment on the role of pharyngeal sensitivity or advancing age as potential predictors or effect modifiers of the primary exposure-outcome relationship. However, we did choose to include pharyngeal sensitivity

and age >55 years as potential predictors in the final model selection based on *a priori* clinical interest and the results of our observational study (75).

Our assessment of pre-procedural anxiety may have been improved by the use of a more rigorous biometric tool than the Hospital Anxiety and Depression Scale (79). This short self-administered questionnaire was developed to detect depression and anxiety in the setting of ambulatory care clinics. Its use in the endoscopic population has been reported by previous authors (77,78); yet, it has not undergone rigorous biometric validation in the GI endoscopic population. Therefore, this tool may not be sufficiently sensitive or specific to adequately detect the anxiety state unique to patient's undergoing diagnostic endoscopy.

A more appropriate biometric instrument may have been the State-Trait Anxiety Inventory (STAI, Consulting Psychologists Press, Palo Alto), the definitive instrument for measuring anxiety in adults (110). It clearly differentiates between the temporary condition of "state anxiety" and the more general and longstanding quality of "trait anxiety", by measuring feelings of apprehension, tension, nervousness and worry. Although not validated for the measurement of pre-endoscopic anxiety, the STAI is widely recognized as the "gold-standard" in the psychological literature, and has been used by previous investigators in the assessment of patients prior to EGDE (113).

4.6.4 Generalizability of Results

Every attempt to ensure a representative sampling of the average Canadian adult ambulatory patient population was taken. These measures

included patient accrual from two general outpatient endoscopy clinics in two separate tertiary care university centers with a diverse multi-ethnic population base and the participation of 18 different endoscopists. We know that the acceptance rate for participation in this study is only 60%. This refusal rate (40%) is on par with other reported refusal rates of 30% (89).

To assess the generalizability of our results, all patients who refused participation in the study were asked to complete the same demographic and anxiety questionnaires as the participating patients, and following their procedure, to rate their satisfaction with their level of comfort during their test. Furthermore, the attending endoscopist was asked to judge the technical adequacy of the procedure, at the completion of EGDE. From this previously published data (107), we know that 80% of those patients who *refused* to be randomized, accepted to complete our questionnaires and to rate their satisfaction with their level of comfort during endoscopy.

When those patients who refused to be randomized were compared to those who agreed, both populations were similar with regard to all baseline characteristics. Only prior EGDE experience was predictive of a patient's refusal to participate in our randomized controlled trial (OR=2.2; 95% CI: 1.3-3.7) (107).

Thus there remains the possibility that the interpretation of our study is limited to the participation of patients who had either no prior gastroscopic experience or a pleasant prior gastroscopic experience. Accordingly, our observations may be conservative because the group that

arguably, might benefit the most from sedation may have refused participation in the trial. This may have contributed to our evidence that prior EGDE experience was not a predictor of successful endoscopy, patient satisfaction alone or willingness to repeat.

4.6.5 Study Implications and Directions for Future Research:

The data analysed in this study represent an interim analysis of an ongoing RCT examining the efficacy and safety of a policy of sedation vs. no sedation in the performance of upper gastrointestinal endoscopy. As such, its results must be interpreted with caution. This study was designed anticipating a small difference in efficacy between the sedated and non-sedated group, suggested previously by European investigators (76-78).

Our interim results (N=360) suggest that the overall proportion of successful endoscopy (one that is both comfortable for the patient and technically adequate) is low (61.4%) secondary to the impact of sedation status on the patient's self-reported comfort. Despite excellent technical adequacy in both randomized groups (98%), patient comfort was only 39.3% among non-sedated patients versus 84% among those patients who received sedation, a difference of 44.7%. Those who are sedated have twice the proportion of successful endoscopy when compared to those who are unsedated (83% vs. 39%). This discrepancy between randomization groups is echoed in the results of willingness to repeat (sedated: 85% vs. unsedated: 59%) and endoscopist satisfaction alone (sedated: 92% vs. unsedated: 71%).

The noted incongruity between our results in a general ambulatory adult population, and those of other investigators (76-78) may be explained by cultural differences between countries and patient expectations. This finding is significant, and has important implications for future cost-effectiveness analysis. In the face of such disparate clinical outcomes, for unsedated EGDE to be cost-effective, the cost incurred by (rare) adverse events plus indirect cost, must greatly outweigh the cost incurred by the delivery of sedated successful endoscopy. This is an important area that merits future research.

Also needed is improved characterization of the population that might best tolerate an unsedated EGDE. With our current results, there still remains the suggestion that the elderly and those with decreased pharyngeal sensitivity might well tolerate unsedated EGDE (Table 3). This may also be the subgroup of patients in whom the cost-benefit ratio for unsedated EGDE is most favorable. However, any future study may require a stratified randomization process to ensure sufficient power in the subgroups of interest. It is unlikely that within the context of the current randomization strategy, sufficient power will be obtained in the subgroups of interest. Thus, the study investigators are now considering premature termination of the trial.

The observation that advancing age may be an important effect modifier of successful endoscopy (Table 3) is particularly important when you consider that it is among the elderly that the risks of cardio-respiratory complications from the sedated gastroscopy, although very low, become most clinically relevant (114). The findings of the present study concur with those of other authors that suggest

upper gastrointestinal endoscopy is well tolerated and safely performed without sedation (84, 99, 103) in seniors. As the Canadian population ages, a substantial proportion of Canadian adult ambulatory patients may be identified as suitable candidates for a comfortable and technically adequate diagnostic gastroscopy, performed without the use of parenteral sedation.

We may see in the future, a decline in the routine use of sedation as our population ages. This potential trend would be consistent with the recent evidence from Britain that reports a 54% decline in the use of sedation for outpatient diagnostic gastroscopy over the last ten years (61). Triaging patients by age and pharyngeal sensitivity may still be useful in predicting which patients can best tolerate an unsedated diagnostic EGDE that is both technically thorough and comfortable for the patient.

Other avenues for future investigation might include the characterization of the effect of smoking on pharyngeal sensitivity and successful endoscopy, and the further quantification of pre-procedural anxiety and its manipulation to ensure successful endoscopy with or without sedation. It has been suggested that tailoring pre-procedural information to individual patient lifestyles may have a beneficial effect on reducing the level of anxiety and improving endoscopic outcomes (115,116). However at this time, this preliminary data is exploratory and must be considered only as hypothesis generating. The magnitude of such an intervention merits future research.

Finally, there is tremendous need for further refinement in our methods of assessing clinical endoscopic outcomes such as patient satisfaction. An

accepted gold-standard method for the assessment of clinical satisfaction with endoscopy is yet to be developed, nor has any previous investigator attempted to define the patient and endoscopic priorities inherent in the performance of a "successful endoscopy". Any such biometric tool must incorporate not only patient satisfaction with their level of comfort (i.e. tolerance of the procedure), but also the technical adequacy of the procedure, as this is an important part of overall test performance.

These patient-centered outcomes (i.e. satisfaction, willingness to repeat) form the basis of clinical outcomes research, and the performance of "successful endoscopy" may become a key quality indicator of the endoscopic service provided (109).

Endoscopic outcome measures become increasingly important in GI endoscopy as diagnostic initiatives intensify in response to the growing prevalence of upper GI complaints caused by dyspepsia, gastroesophageal reflux disease and dysphagia (100). The development of outcome measurement instruments, which can then be universally applied, is also an important area of future research in endoscopy. Once developed, investigators will be better equipped to compare competing sedation strategies as they relate to the performance diagnostic or therapeutic endoscopy.

4.7 Conclusions

The interim analysis of this double blind, randomized, placebo-controlled trial, has shown that the use of parenteral sedation improves the efficacy of

diagnostic EGDE in the adult ambulatory population in a Canadian tertiary health care center. The routine use of routine sedation does not improve technical adequacy, but does contribute to increased: successful endoscopy, patient satisfaction and willingness to repeat in all patients, without a concomitant increase in adverse cardio-pulmonary events.

Based on our findings and that published in the existing literature, we recommend that those patients less than 55 years of age, with increased pharyngeal sensitivity, high pre-procedural anxiety and negative expectations of their forthcoming EGDE be offered routine parenteral sedation prior to diagnostic EGDE. The elderly, and those patients with decreased pharyngeal sensitivity; minimal pre-procedural anxiety and positive expectations may be able to tolerate unsedated diagnostic EGDE. Accordingly, they should be offered that opportunity to minimize the risk of (rare) adverse events and the inconvenience incurred by the routine use of parenteral sedation for a diagnostic procedure.

5. ACKNOWLEDGEMENTS

I would like to acknowledge the following friends and colleagues who provided moral support and material assistance in the collection, analysis, interpretation and preparation of the original data required for the completion of this thesis. My thesis committee, including my supervisor, Dr. Jean-Paul Collet, Dr. Alan Barkun for his mentorship and collaboration during the development and execution of this randomized controlled trial, and Dr. Nandini Dendakuri.

Dr. Carlo Fallone, Dr. Serge Mayrand, Dr. Lawrence Joseph, Mr. Patrick Belisle, Ms. Vicky Thiffault, Ms. Dalila Benhaberou-Brun, Mr. Paul Wieczorek, Mr. Jack Huang and the members of the GI division of the McGill University Health Centre for their assistance in the recruitment of patients, data input and the preliminary analysis of the pilot study. The Canadian Association of Gastroenterology, Carsen Group and the Canadian Institute for Health Research who funded my research training over two years. Finally, I would like to acknowledge the support and faith of my family and friends.

6. REFERENCES:

1. Health and public policy committee of ACP. Clinical competence in diagnostic esophagogastroduodenoscopy. Ann Int Med 1987; 107:937-9.
2. Scott BB. Gastroenterology in the Trent region in 1992 and a review of changes since 1975. Gut 1995; 36:468-72.
3. Lalor E, Thomson AB. Comparison of the utilization of endoscopy units in selected teaching hospitals across Canada. Can J Gastroenterol 1996; 10:381-4.
4. Froehlich F, Gonvers JJ, Fried M. Conscious sedation, clinically relevant complications, and monitoring of endoscopy: results of a nationwide survey in Switzerland. Endoscopy 1994; 26:231-4.
5. Lieberman DA, Wuerker CK, Katon RM. Cardiopulmonary risk of esophagogastroduodenoscopy. Role of endoscopic diameter and systemic sedation. Gastroenterology 1985; 88:468-72.
6. Keefe EB, Schrock TR. Complications of gastrointestinal endoscopy. In: MH S, ed. Sleisenger and Fordtran. Vol. 1. Philadelphia: Saunders, WB, 1993:301-8.
7. Fleischer D. Monitoring for sedation: perspective of the gastrointestinal endoscopist. Gastroenterol Endosc 1990; 36:S19-22.
8. Bailey RJ, Barkun A, Brow J et al. Consensus in Endoscopy. Can J Gastroenterol 1996; 10:237-42.

9. Keefe E, O'Connor K. 1989 ASGE survey of endoscopic sedation and monitoring practices. Gastroenterol Endosc. 1990; 36:S13-8.

10. Hoare AM, Hawkins CF. Upper gastrointestinal endoscopy with and without sedation: patients' opinions. Brit Med J 1976; 1:20-31.

11. Al-Altrakchi HA. Upper gastrointestinal endoscopy without sedation: a prospective study of 2000 examinations. Gastrointest Endosc 1989; 35:120-5.

12. Hedenbro JL, Lindblom A. Patient attitudes to sedation for diagnostic upper endoscopy. Scand J Gastroenterol 1991; 26:1115-1120.

13. Pereira SP, Hussaini SH, Hanson PJV et al. Endoscopy: throat spray or sedation? The Journal of the Royal College of Physicians of London 1994; 28:411-14.

14. Modlin I. A brief history of endoscopy. In: Modlin IM, ed. Vol. 1. Milano: MultiMed, 1999:144.

15. Morrissey J, Reichelderfer M. Gastrointestinal endoscopy. NEJM 1991; 325:11422-1149 and 1214-1222.

16. Lieberman DA, De Garmo PL, Fleischer DE, Eisen GM, Helfand M. Patterns of Endoscopy Use in the United States. Gastroenterology 2000; 118:619-624.

17. Modlin I. A Brief History of Endoscopy. Milano: MultiMed, 2000:144.

18. Haubrich W. The centennial year: The development of important ideas during the last 100 years. The advent and evolution of endoscopy. Gastroenterology 1997; 112:591.

19. Zuccaro G. Sedation and Sedationless Endoscopy. Gastrointestinal Endoscopy Clinics of North America 2000; 10:1-20.

20. Mokhashi M, Hawes R. Struggling toward easier endoscopy. Gastrointestinal Endoscopy 1998; 48:432-438.

21. Drossman D, Brandt L, Sears C, al. e. A preliminary study of patients' concerns related to GI endoscopy. Am J Gastroenterol 1996; 91:287-291.

22. Probert C, Jayanthi V, Quinn J, Mayberry J. Information requirements and sedation preferences of patients undergoing endoscopy of the upper gastrointestinal tract. Endoscopy 1991; 23:218-219.

23. Daneshmend T, Bell G, Logan R. Sedation for upper gastrointestinal endoscopy: Results of a nationwide survey. GUT 1991; 32:12-15.

24. Diab F, King P, Barthel J, Marshall J. Efficacy and safety of combined meperidine and midazolam for EGDE sedation compared with midazolam alone. Am J Gastroenterol 1996; 91:1120-1125.

25. Carrougher J, Kadakia S, Shaffer R, Barrilleaux C. Venous complications of midazolam versus diazepam. Gastrointest Endosc 1993; 39:396-399.

26. Mahajan R, Johnson J, Marshall J. Predictors of patient cooperation during gastrointestinal endoscopy. J Clin Gastroenterol 1997; 24:220-223.

27. Van Houten J, Crane S, Janardan S, Wells K. A randomized, prospective, double blind comparison of midazolam (Versed) and emulsified diazepam (Dizac) for opioid based, conscious sedation endoscopic procedures. Am J Gastroenterol 1998; 93:170-174.

28. Ginsberg G, Lewis J, Gallagher J, al. e. Diazepam versus midazolam for colonoscopy: A prospective evaluation of predicted versus actual dosing requirements. Gastrointest Endosc 1992; 38:651-656.

29. Bell G, Spickett G, Reeve P, al. e. Intravenous midazolam: A study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy. Br J Clin Pharmacol 1992; 23:241-243.

30. Scholer S, Schafer D, Potter J. The effect of age on the relative potency of midazolam and diazepam for sedation in upper gastrointestinal endoscopy. J Clin Gastroenterol 1990; 12:145-147.

31. Sparberg M, Knudsen K. Is local anesthesia necessary in fiberoptic esophagogastroscopy? Am J Dig Dis 1967; 12:1131-3.

32. Cantor D, Baldridge E. Premedication with meperidine and diazepam for upper gastrointestinal endoscopy precludes the need for topical anesthesia. Gastrointest Endosc 1986; 32:339-41.

33. Chuah S, Croson C, Dronfield M. Topical anesthesia in upper gastrointestinal endoscopy. BMJ 1991; 303:695.

34. Daniel E, Michael P, Craig M. Topical pharyngeal anesthesia does not improve upper gastrointestinal endoscopy in conscious sedated patients. Am J Gastroent 1999; 94:1853-6.

35. Gordon M, Mayes G, Meyer G. Topical lidocaine in pre-endoscopic medication. Gastroenterology 1976; 71:564-9.

36. Jameson J, Kapadia S, Polson R, McCarthy P, Misiewicz J. Topical anesthesia improves toleration for upper gastrointestinal endoscopy [abstract]. Gut 1992; 33:203.

37. Hedenbro J, Ekelund M, Jansson O, Lindblom A. A randomized, double blind, placebo-controlled study to evaluate topical anesthesia of the pharynx in upper gastrointestinal endoscopy. Endoscopy 1992; 24:585-7.

38. Leitch D, Wicks J, Osama A, et al. Topical anesthesia with 50 mg of lidocaine spray facilitates upper gastrointestinal endoscopy. Gastroint Endosc 1993; 39:384-7.

39. Lachter J, Jacobs R, Lavy A, et al. Topical anaesthesia for easing endoscopy: a double-blind, randomized, placebo-controlled study. Gastrointestinal Endosc 1990; 36:19-21.

40. Soma Y, Saito H, Kishibe T, al. e. Evaluation of topical pharyngeal anesthesia for upper endoscopy including factors associated with patient tolerance. Gastroint Endosc 2001; 53:14-18.

41. Davis D, Jones M, Kubik C. Topical pharyngeal anesthesia does not improve upper gastrointestinal endoscopy in conscious sedated patients. Am J Gastroenterol 1999; 94:1853-56.

42. Archimandritis A, Tjivras M, Tryphonos M, Delikaris P, Diamantis T. Is premedication necessary in diagnostic endoscopy of the upper gastrointestinal tract? Endoscopy 1991; 23:240.

43. Zimmerman J, Rachmilewitz D. Systemic anaphylactic reaction following lidocaine administration. Gastrointest Endosc 1985; 31:404-5.

44. Patel D, Chopra S, Berman M. Serious systemic toxicity resulting from use of tetracaine for pharyngeal anesthesia in upper endoscopic procedures. Dig Dis Sci 1989; 34:882-4.

45. Grum D, Rice T. Methemoglobinemia from topical benzocaine. Clev Clin J Med 1990; 57:357-9.

46. Buckley A, Newman A. Methemoglobinemia occurring after the use of a 20% benzocaine topical anesthetic prior to gastroscopy. Gastrointest Endosc 1987; 33:466-7.

47. O'Donohue WJ, Moss L, Angelillo V. Acute methemoglobinemia induced by topical benzocaine and lidocaine. Arch Intern Med 1980; 140:1508-9.

48. Collins J. Methemoglobinemia as a complication of 20% benzocaine spray for endoscopy. Gastroenterology. 1990; 98:211-3.

49. Brown C, Levy S, Susann P. Methemoglobinemia: life-threatening complication of endoscopy premedication. Am J Gastroenterol 1994; 89:1108-9.

50. Dinneen S, Mohr D, Fairbanks V. Methemoglobinemia from topically applied anesthetic spray. Mayo Clin Proc 1994; 69:886-8.

51. Quine M, Bell G, McCloy R, Charlton J, Devlin H, Hopkins A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: Safety, staffing and sedation method. Gut 1995; 36:462-7.

52. Arrowsmith A, Gerstman B, Fleischer D, Benjamin S. Results from the American Society for Gastrointestinal Endoscopy/ US Food and Drug

Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. Gastrointest Endosc 1991; 37:421-7.

53. Campo R, Brullet E, Montserrat A, Calvet X, Rivero E, Brotons C. Topical Pharyngeal Anesthesia Improves Tolerance of Upper Gastrointestinal Endoscopy: A Randomized Double-Blind Study. Endoscopy 1995; 27:659-664.

54. Smith J, Opekun A, Graham D. Controlled comparison of topical anesthetic agents in flexible upper gastrointestinal endoscopy. Gastroint Endosc 1985; 31:255-58.

55. Goodman L, Gilman A. The pharmacological basis of therapeutics. In: Goodman L, Gilman A, eds. New York: MacMillan, 1969:268.

56. Keefe E. Complications of gastrointestinal endoscopy. In: Sleisenger M, Fordtran J, eds. Gastrointestinal Disease. Philadelphia: WB Saunders Co., 1993:301-8.

57. Carey W. Indications, contraindications and complications of upper gastrointestinal endoscopy. In: Sivak Jr. M, ed. Gastroenterologic Endoscopy. Philadelphia: WB Saunders Co., 1987:868-80.

58. Gilbert D, Silverstein F, Tedesco F, al. e. National ASGE survey on upper gastrointestinal bleeding, complications of endoscopy. Dig Dis Sci 1981; 26:55-9.

59. Bell G, Spickett G, Reeve P, al. e. Intravenous midazolam for upper gastrointestinal endoscopy: a study of 800 consecutive cases relating dose to age and sex of patient. Br J Clin Pharmacol 1987; 23:241-3.

60. Ben-Shlomo I, Abd-El-Khalim H, Ezry J, al. e. Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth 1990; 64:45-7.

61. Mulcahy H, Hennessy E, Connor P, et al. Changing patterns of sedation use for routine outpatient diagnostic gastrosocopy between 1989 and 1998. Aliment Pharmacol Ther 2001; 15:217-220.

62. Anonymous. Monitoring of patients undergoing gastrointestinal endoscopic procedures.: ASGE publication, 1989.

63. Anonymous. Sedation and Monitoring of Patients undergoing Gastrointestinal Endoscopic Procedures. Manchester, Massachusetts: ASGE, 1995:10.

64. The council on Scientific Affairs AMA. The use of pulse oximetry during conscious sedation. JAMA 1993; 270:1463-8.

65. Bell G, Brown S, Morden A, al. e. Prevention of hypoxemia during upper gastrointestinal endoscopy by means of oxygen via nasal cannulae. Lancet 1987; 1:1022-24.

66. Griffin S, Chung S, Leung J, al. e. Effect of intranasal oxygen on hypoxia and tachycardia during endoscopic cholangiopancreatography. Br Med J 1990; 300:83-4.

67. Freeman M, Hennessy J, Cass O, Pheley A. Carbon dioxide retention and oxygen desaturation during gastrointestinal endoscopy. Gastroenterology 1993; 105:331-9.

68. Murray A, Morran C, Kenny G, al. e. Arterial oxygen saturation during upper gastrointestinal endoscopy: the effects of a midazolam/pethidine combination. Gut 1990; 31:270-3.

69. Gross J, Bailey P, Cote C, al. e. American Society of Anesthesiologists guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 1996; 84:459-71.

70. Bowton D, Scuderi P, Harris L, Haponik E. Pulse oximetry monitoring outside the Intensive Care Unit: progress or problem? Ann Intern Med 1991; 115:450-54.

71. Fassoulaki A, Mihas A. changes in arterial blood gases associated with gastrointestinal endoscopies. Acta Anaesthesiol Belg 1987; 38:127-31.

72. Barkin J, Krieger B, Blinder M, al. e. Oxygen desaturation and changes in breathing pattern in patients undergoing colonoscopy and gastroscopy. Gastroint Endosc 1989; 35:526-530.

73. Gombar K, Dhall J, Suri R, al. e. Effect of diazepam sedation on arterial oxygen saturation during esophagogastroduodenoscopy: A placebo-controlled study. Indian J Gastroenterol 1992; 15:40-42.

74. Dark D, Campbell D, Wesselius L. Arterial oxygen desaturation during gastrointestinal endoscopy. Am J Gastroenterol 1990; 85:1317-1321.

75. Abraham N, Barkun A, Larocque M, et al. Predicting which patients can undergo a gastroscopy comfortably without the need for conscious sedation. Gastro Endosc (in press) 2002.

76. Froehlich F, Schwizer W, Thorens J, Kohler M, Gonvers J, Fried M. Sedation for gastroscopy: Patient tolerance and cardiorespiratory parameters. Gastroenterology 1995; 108:697-704.

77. Schutz S, Lee J, Schmidt C, Almon M, Baillie J. Clues to patient dissatisfaction with sedation for colonoscopy. American Journal of Gastroenterology 1994; 89:1476-9.

78. Schutz S, Lee J, Schmidt C, Baillie J. Patient satisfaction with sedation for endoscopy. Gastrointest Endosc 1994; 40:119-20.

79. Zigmond A, Snaith R. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361-70.

80. Jennison C, Turnbull BW. Interim analyses: The repeated confidence interval approach (with discussion). Journal of the Royal Statistical Society B 51(3): 305-61.

81. Waye J. Worldwide use of sedation and analgesia for upper intestinal endoscopy. Gastroint Endosc 1999; 50(6): 888-91.

82. Ross WA. Premedication for upper gastrointestinal endoscopy. Gastrointest Endosc 1989; 35: 120-5.

83. Fisher NC, Bailey S, Gibson JA. A Prospective randomized controlled trial of sedation vs. no sedation in outpatient diagnostic upper gastrointestinal endoscopy. Endoscopy 1998; 30: 21-24.

84. Sorbi D, Gostout CJ, Henry J et al. Unsedated small-caliber esophagogastroduodenoscopy (EGDE) versus conventional EGDE: a comparative study. Gastroenterology 1999; 117: 1301.

85. Rey JF. Sedation for upper gastrointestinal endoscopy: as much as possible, or without? Endoscopy 1996; 28: 308-9.

86. Pound DC, O'Connor KW, Brown ED, Weddle R, McHenry et al. Oral medications for upper gastrointestinal endoscopy using a small diameter endoscope. Gastroint Endosc 1988; 34(4): 327-331.

87. Jameson JS, Kapadia SA, Polson RJ, McCarthy PT, Misiewicz JJ. Is oropharyngeal anaesthesia with topical lignocaine useful in upper gastrointestinal endoscopy? Alimentary Pharmacology and Therapeutics 1992; 6: 739-44.

88. Mulcahy HE, Greaves RRSH, Ballinger A, Patchett SE, Riches A et al. A double blind randomized trial of low-dose versus high-dose topical anaesthesia in unsedated upper gastrointestinal endoscopy.

89. Zaman A, Hahn M, Hapke R, Knigge K, Fennerty B, Katon RM. A randomized trial of peroral versus transnasal unsedated endoscopy using an ultrathin videoendoscope. Gastroint Endosc 1999; 49: 279-284.

90. Campo R, Montserrat A, Brullet E. Transnasal gastroscopy compared to conventional gastroscopy: a randomized study of feasibility, safety, and tolerance. Endoscopy 1998; 30: 449-452.

91. Dumortier J, Ponchon T, Scoazec JY, Moulinier B, Zarka F et al. Prospective evaluation of transnasal esophagogastroduodenoscopy: feasibility and study on performance and tolerance. Gastroint Endosc 1999; 49: 285-291.

92. Christe C, Janssens JP, Armenian, B, Herrmann F, Vogt N. Midazolam sedation for upper gastrointestinal endoscopy in older persons: a randomized, double blind placebo-controlled study. Journal of the American Geriatrics Society 2000; 48: 1398-1403.

93. Thompson AM, Park KGM, Kerr F, Munro A. Safety of fibreoptic endoscopy: analysis of cardiorespiratory events. Br J Surg 1992; 79: 1046-1049.

94. Dhir V, Swaroop VS, Vazifdar KF, Wagle SD. Topical pharyngeal anesthesia without intravenous sedation during upper gastrointestinal endoscopy. Indian Journal of Gastroenterology 1997; 16: 10-1.

95. Shua-Haim JR, Gross JS. Methemoglobinemia toxicity from topical benzocaine spray. Journal of the American Geriatrics Society 1995; 43:590.

96. Gunaratnam NT, Vazquez-Sequeiros E, Gostout CJ, Alexander GL. Methemoglobinemia is related to topical benzocaine use: is it time to reconsider the empiric use of topical anesthesia before sedated EGDE? Gastroint Endosc 2000; 52: 692-3.

97. Zuberi BF, Shaikh MR, Jatoi NU, Shaikh WM. Lidocaine toxicity in a student undergoing upper gastrointestinal endoscopy. Gut 2000; 46: 435.

98. Martin JP, Arlett PA, Holdstock G. Development of a sedation policy for upper GI endoscopy based on an audit of patient's perception of the procedure. Eur J Gastroenterol Hepatol 1996; 8: 355-7.

99. Tan CC, Freeman JG. Throat spray for upper gastrointestinal endoscopy is quite acceptable to patients. Endoscopy 1996; 28: 277-282.

100. Shaker R. A wake-up call? Unsedated versus conventional esophagogastroduodenoscopy [editorial]. Gastroenterology 2000; 117(6): 1492-95.

101. Woloshynowich M, Oakley DA, Sauders BP, Williams CB. Psychological aspects of gastrointestinal endoscopy: a review. Endoscopy 1996; 28: 763-7.

102. Campo R, Brullet E, Montserrat A et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. European Journal of Gastroenterology and Hepatology 1999; 11:201-4.

103. Zaman A, Hapke R, Sahagun G et al. Unsedated peroral endoscopy with a video ultrathin endoscope: patient acceptance, tolerance and diagnostic accuracy. Am J Gastroenterol 1998; 93: 1260-63.

104. Walmsley RS, Montgomery SM. Factors affecting patient tolerance of upper gastrointestinal endoscopy. J Clin Gastroenterol 1998; 26(4): 253-55.

105. Gelly AL, Farley A, Boyer J, Asselin M, Spenard J. Influence of sex, age and smoking status on patient comfort during gastroscopy with pharyngeal anesthesia by a new benzocaine-tetracaine preparation. Can J Gastroenterol 1998; 12(6): 431-433.

106. Davies AE, Kidd D, Stone SP, MacMahon J. Pharyngeal sensation and gag reflex in healthy subjects. Lancet 1995; 345: 487-88.

107. Abraham NS, Wieczorek P, Huang J, Mayrand S, Barkun AN. Assessing Bias in Sedation Studies. Gastrointest Endosc. 2000;51:AB75.

108. Davies AR, Ware JE Jr. GHAA's consumer satisfaction survey and user's manual. Washington, DC: Group Health Association of America; 1991.

109. Yacavone R, Locke G, Gostout C, Rockwood T et al. Factors influencing patient satisfaction with GI endoscopy. Gastroint Endosc 2001; 53(7): 703-10.

110. Spielberger CD. Manual for the State-Trait Anxiety Inventory (STAI). Palo Alto CA. 1983:Consulting Psychologists Press.

111. Craig A, Hanlon J, Dent J, Schoeman M. A comparison of transnasal and transoral endoscopy with small-diameter endoscopes in unsedated patients. Gastroint Endosc 1999; 49(3): 292-6.

112. LaLuna L, Allen M, DiMarino A. The comparison of midazolam and topical lidocaine spray versus the combination of midazolam, meperidine, and topical lidocaine spry to sedate patients for upper endoscopy. Gastroint Endosc 2001; 53(3): 289-93.

113. Dumitrascu DL, Pascu O, Wienbeck M. Re: Anxiety in patients submitted to endoscopy [letter]. AJG 1997; 92(8): 1403-4.

114. McAlpine JK, Martin BJ, Devine BL. Cardiac arrythmias associated with upper gastrointestinal endoscopy in elderly subjects. Scott Med J 1990; 35:102-4.

115. Owen FD, Felts JA, Spitznagel EL Jr, et al. ASA physical status classification: a study of consistency of ratings. Anaesthesiology 1978; 49:239-43.

116. Kass R, Raftery A. Bayes Factors. Jour of Am Statistical Assoc 1995; 90:773-795.

7. APPENDICES

Table 1: Frequency of Baseline Characteristics Among Randomized Groups

Variable	Sedated N (%)	Non-Sedated N (%)
Total	x (100%)	y (100%)
Gender		
Male	87 (48%)	87 (49%)
Female	94 (52%)	90 (51%)
Age1		
<35 years	34 (19%)	16 (9%)
35-55 years	64 (35%)	62 (35%)
55-75 years	68 (37%)	75 (42%)
> 75 years	16 (9%)	25 (14%)
Caucasian	152 (84%)	146 (82%)
Education		
<High School	20 (11%)	18 (10%)
High Scool only	63 (18%)	117 (33%)
College (CEGEP)	38 (11%)	32 (18%)
University	59 (33%)	61 (34%)
Smoker	32 (18%)	24 (14%)
Anxious	73 (41%)	80 (45%)
Treatment for an Anxiety Disorder	17 (9%)	15 (8%)
Regular Use of Prescription Sedatives	18 (10%)	15 (9%)
Regular Use of Prescription Analgesics	17 (9%)	19 (11%)
Regular Use of Prescription Anxiolytics	20 (11%)	15 (8%)
Dyspepsia	103 (57%)	120 (67%)
Prior EGD experience	80 (44%)	90 (51%)
Expectations of the procedure		
1=Acceptable	92 (51%)	73 (42%)
2=	41 (23%)	54 (31%)
3=	41 (23%)	41 (23%)
4=	5 (3%)	6 (3%)
5=Unacceptable	1 (0.6%)	2 (1%)

Table 1: Frequency of Baseline Characteristics Among Randomized Groups

Variable	Sedated N (%)	Non-Sedated N (%)
Pharyngeal Sensitivity		
1= not sensitive	106 (61%)	86 (50%)
2=	34 (19%)	36 (21%)
3=	15 (9%)	20 (12%)
4=	7 (4%)	17 (10%)
5 = extremely sensitive	13 (7%)	12 (7%)
Sensitive Pharynx	35 (20%)	49 (29%)
EGD scope size=9.8 mm	171 (95%)	165 (95%)
Procedure performed by non-physician	167 (92%)	160 (90%)
Biopsy performed during EGD	148 (81%)	138 (78%)
Technical Adequacy Score of EGD	180 (99%)	173 (97%)

Table 2: Clinical Predictors of Successful Endoscopy

Variable		Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Sedation				
	*Non-Sedated**	1.0	0.0	
	Sedated	7.52	0.46	<0.001
		(4.61-12.26)	(0.36-0.55)	
Expectations				
	*Negative**	1.0	0.0	
	Positive	2.07	0.15	0.0024
		(1.29-3.34)	(0.05-0.24)	
Anxiety				
	*Not-Anxious**	1.0	0.0	
	Anxious	0.68	0.1	0.0799
		(0.44-1.05)	(-0.20-0.01)	
Dyspepsia				
	*No**	1.0	0.0	
	Yes	0.67	0.09	0.0783
		(0.43-1.05)	(-0.19-0.009)	
Pharyngeal Sensitivity				
	*No**	1.0	0.0	
	Yes	0.66	0.08	0.0959
		(0.40-1.08)	(-0.17-0.02)	
Age >55				
	*No**	1.0	0.0	
	Yes	1.39	0.04	0.1271
		(0.91-2.13)	(-0.05-0.14)	
Gender				
	*Male**	1.0	0.0	
	Female	0.79	0.06	0.2704
		(0.52-1.21)	(-0.17-0.05)	
Education <High School				
	*No**	1.0	0.0	
	Yes	1.9	0.06	0.0915
		(0.89-4.05)	(-0.005-0.12)	
High School Only				
	*No**	1.0	0.0	
	Yes	0.94	0.01	0.7925
		(0.61-1.47)	(-0.12-0.09)	
CEGEP Only				
	*No**	1.0	0.0	
	Yes	0.82	0.03	0.453
		(0.48-1.39)	(-0.12-0.05)	

Table 2: Clinical Predictors of Successful Endoscopy

Variable		Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
University Only				
	*No**	1.0	0.0	
	Yes	0.93	0.02	0.7691
		(0.60-1.47)	(-0.12-0.09)	
Heartburn				
	*No**	1.0	0.0	
	Yes	0.64	0.11	0.0439
		(0.42-0.99)	(0.004-0.21)	
Vomiting				
	*No**	1.0	0.0	
	Yes	0.7	0.05	0.2216
		(0.39-1.25)	(-0.13-0.03)	
Ulcer				
	*No**	1.0	0.0	
	Yes	1.22	0.03	0.4817
		(0.70-2.11)	(-0.05-0.11)	
Indigestion				
	*No**	1.0	0.0	
	Yes	0.79	0.05	0.2858
		(0.51-1.22)	(-0.16-0.05)	
Dysphagia				
	*No**	1.0	0.0	
	Yes	0.77	0.04	0.3661
		(0.44-1.36)	(-0.12-0.04)	
Endoscopist				
	*Resident**	1.0	0.0	
	Staff	0.9	0.009	0.0774
		(0.43-1.89)	(-0.07-0.05)	
Smoker				
	*No**	1.0	0.0	
	Yes	1.53	0.05	0.1703
		(0.83-2.83)	(-0.02-0.13)	
Prior History of EGDE				
	*No**	1.0	0.0	
	Yes	1.14	0.03	0.54
		(0.75-1.75)	(-0.14-0.07)	

** Reference category*

Table 3: Stratified Analysis of Clinical Predictors of "Successful Endoscopy"

Variable		N/strata	OR	95% CI	Breslow-Day Test (p<0.2)	Common OR
Age>55						
	*No**	176	7.32	3.7-14.3	0.53	8.5
	Yes	184	10.19	4.6-22.6		(5.1-14.9)
Age >65						
	*No**	250	7.5	4.2-13.3	0.83	7.8
	Yes	108	8.5	3.1-23.0		(4.7-12.7)
Age>75						
	*No**	319	8.54	5.1-14.4	0.24	7.65
	Yes	41	3.4	0.77-15.0		(4.7-12.5)
Anxious						
	*No**	202	11.96	5.8-24.7	0.13	
	Yes	153	5.49	2.7-11.1		
Education: <High School						
	*No**	319	7.66	4.6-12.8	0.95	7.6
	Yes	38	7.2	1.2-40.7		(4.7-12.5)
Pharyngeal Sensitivity						
	*No**	262	8.74	4.9-15.8	0.12	
	Yes	84	3.63	1.4-9.2		
Dyspepsia						
	*No**	137	5.33	2.5-11.6	0.3	7.4
	Yes	223	9.06	4.8-17.2		(4.5-12.0)
Prior EGDE						
	*No**	189	11.4	5.7-22.9	0.1	
	Yes	170	5	2.5-10.0		
Gender						
	*Male**	174	5.64	2.8-11.3	0.28	7.4
	Female	184	9.75	4.9-19.5		(4.5-12.1)
Smoker						
	*No**	302	9.02	5.2-15.6	0.05	
	Yes	56	2.55	0.8-8.2		
Positive Expectations						
	*No**	96	9	3.6-22.7	0.09	
	Yes	260	7.6	4.1-14.0		
Staff Endoscopist						
	*No**	33	2.2	0.5-9.6	0.08	
	Yes	327	8.6	5.1-45.6		
Biopsy Performed						
	*No**	74	10.9	3.6-33.1	0.45	7.5
	Yes	286	6.8	3.9-11.7		(4.6-12.2)

**Reference Category*

Table 4: Clinical Predictors of Willingness To Repeat

Variable	Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Sedation			
*Non-Sedated**	1.0	0.0	
Sedated	3.8 (2.3-6.4)	0.32 (0.21-0.43)	<0.001
Expectations			
*Negative**	1.0	0.0	
Positive	1.32 (0.79-2.21)	0.06 (-0.05-0.16)	0.2881
Anxiety			
*Not-Anxious**	1.0	0.0	
Anxious	0.76 (0.47-1.21)	0.07 (-0.05-0.19)	0.2404
Dyspepsia			
*No**	1.0	0.0	
Yes	0.45 (0.27-0.76)	0.17 (0.07-0.28)	0.0025
Pharyngeal Sensitivity			
*No**	1.0	0.0	
Yes	0.66 (0.40-1.13)	0.08 (-0.03-0.19)	0.1286
Age >55			
*No**	1.0	0.0	
Yes	1.06 (0.67-1.70)	0.02 (-0.13-0.10)	0.7924
Age>65			
*No**	1.0	0.0	
Yes	0.92 (0.56-1.5)	0.02 (-0.09-0.13)	0.7544
Age>75			
*No**	1.0	0.0	
Yes	0.8 (0.4-1.6)	0.02 (-0.05-0.10)	0.5403
Gender			
*Male**	1.0	0.0	
Female	0.43 (0.26-0.69)	0.21 (0.09-0.32)	0.0005
Education <High School			
*No**	1.0	0.0	
Yes	1.46 (0.64-3.31)	0.03 (-0.3-0.10)	0.37

High School Only				
	*No**	1.0	0.0	
	Yes	0.88	0.03	0.6019
		(0.54-1.43)	(-0.08-0.14)	
CEGEP Only				
	*No**	1.0	0.0	
	Yes	0.65	0.07	0.1312
		(0.37-1.14)	(-0.03-0.17)	
University Only				
	*No**	1.0	0.0	
	Yes	1.34	0.06	0.2585
		(0.81-2.21)	(-0.04-0.17)	
Heartburn				
	*No**	1.0	0.0	
	Yes	0.64	0.11	0.0439
		(0.42-0.99)	(0.004-0.21)	
Endoscopist				
	*Resident**	1.0	0.0	
	Staff	1.34	0.03	0.4462
		(0.63-2.89)	(-0.05-0.10)	
Smoker				
	*No**	1.0	0.0	
	Yes	1.27	0.03	0.4787
		(0.65-2.49)	(-0.05-0.11)	
Prior History of EGDE				
	*No**	1.0	0.0	
	Yes	1.21	0.03	0.4234
		(0.76-1.93)	(-0.14-0.07)	
Time to Perform Endoscopy (Dichotomized at median= 317.5 sec	317.5 sec*	0.78	0	0.2908
	>317.5 sec	(0.49-1.24)	0.06	
			(-0.09-0.08)	

** Reference category*

Table 5: Clinical Predictors of Patient Satisfaction Alone

Variable	Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Sedation			
*Non-Sedated**	1.0	0.0	
Sedated	9.53 (4.55-19.96)	0.46 (0.36-0.56)	<0.001
Expectations			
*Negative**	1.0	0.0	
Positive	2.04 (1.16-3.58)	0.15 (0.02-0.28)	0.0117
Anxiety			
*Not-Anxious**	1.0	0.0	
Anxious	0.82 (0.48-1.39)	0.05 (-0.08-0.18)	0.4633
Dyspepsia			
*No**	1.0	0.0	
Yes	0.74 (0.42-1.29)	0.07 (-0.05-0.19)	0.2822
Pharyngeal Sensitivity			
*No**	1.0	0.0	
Yes	0.58 (0.33-1.05)	0.11 (-0.02-0.23)	0.0688
Age >55			
*No**	1.0	0.0	
Yes	1.41 (0.83-2.40)	0.09 (-0.05-0.22)	0.2002
Elderly (>65 yrs)			
*No**	1.0	0.0	
Yes	1.14 (1.64-2.05)	0.03 (-0.09-0.15)	0.6567
Old Age(>75yrs)			
No*	1.0	0.0	
Yes	1.15 (0.49-2.71)	0.014 (-0.07-0.09)	0.7524

Table 5: Clinical Predictors of Patient Satisfaction Alone

Variable		Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Gender				
	*Male**	1.0	0.0	
	Female	0.51	0.164	0.0147
		(0.29-0.88)	(0.04-0.29)	
Education				
<High School				
	*No**	1.0	0.0	
	Yes	4.7	0.09	0.0221
		(1.10-20.0)	(0.04-0.15)	
Endoscopist				
	*Resident**	1.0	0.0	
	Staff	1.17	0.01	0.7205
		(0.49-2.83)	(-0.07-0.09)	
Smoker				
	*No**	1.0	0.0	
	Yes	2.64	0.1	0.0409
		(1.00-6.88)	(0.02-0.18)	
Prior History of EGDE				
	*No**	1.0	0.0	
	Yes	1.58	0.11	0.0944
		(0.92-2.72)	(-0.02-0.24)	

** Reference category*

Table 6: Clinical Predictors of Endoscopist Satisfaction Alone

Variable	Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Sedation			
*Non-Sedated**	1.0	0.0	
Sedated	4.95 (2.63-9.33)	0.38 (0.28-0.48)	<0.0001
Expectations			
*Negative**	1.0	0.0	
Positive	0.7 (0.37-1.33)	0.04 (-0.06-0.15)	0.2754
Anxiety			
*Not-Anxious**	1.0	0.0	
Anxious	1.03 (0.60-1.78)	0.06 (-0.05-0.18)	0.9024
Dyspepsia			
*No**	1.0	0.0	
Yes	0.78 (0.44-1.37)	0.06 (-0.05-0.17)	0.3819
Pharyngeal Sensitivity			
*No**	1.0	0.0	
Yes	0.63 (0.35-1.14)	0.14 (0.03-0.25)	0.1263
Age >55			
*No**	1.0	0.0	
Yes	1.23 (0.72-2.09)	0.1 (-0.009-0.22)	0.4564
Elderly (>65 yrs)			
*No**	1.0	0.0	
Yes	1.08 (0.60-1.95)	0.08 (-0.02-0.18)	0.7868
Old Age (>75 yrs)			
*No**	1.0	0.0	
Yes	1.35 (0.54-3.36)	0.06 (0.0005-0.13)	0.5155
Gender			
*Male**	1.0	0.0	
Female	0.99 (0.58-1.70)	0.04 (-0.07-0.16)	0.983
Education <High School			
*No**	1.0	0.0	
Yes	1.0 (0.42-2.39)	0.01 (-0.06-0.08)	0.9911

Table 6: Clinical Predictors of Endoscopist Satisfaction Alone

Variable	Odds Ratio (95% CI)	Risk Difference (95% CI)	Chi-Square Probability
Endoscopist			
*Resident**	1.0	0.0	
Staff	0.99	0.006	0.9812
	(0.39-2.50)	(-0.06-0.07)	
Smoker			
*No**	1.0	0.0	
Yes	1.22	0.02	0.6193
	(0.56-2.62)	(-0.07-0.10)	
Prior History of EGDE			
*No**	1.0	0.0	
Yes	1.02	0.02	0.9449
	(0.60-1.74)	(-0.09-0.14)	
Time to Perform EDGE			
*<317.5 sec**	1.0	0.0	
>317.5 sec	0.51	0.17	0.0142
	(0.29-0.88)	(0.06-0.28)	

** Reference category*

Appendix 1: Model Selection for Successful Endoscopy

	Model	Beta Estimate for Sedation	Standard Error of Beta Estimate (Sedation)	P-Value	OR For Sedation (95% CI)	BIC	Log Likelihood Test
1	Sedation	2.02	0.25	<0.0001	7.5 (4.6-12.4)	416.5	404.7
2	Sedation, Age >55	2.13	0.26	<0.0001	8.4 (5.0-14.2)	415.1	397.5
3	Sedation, Age (continuous)	2.19	0.27	<0.0001	8.9 (5.3-15.0)	410.7	393.1
4	Sedation, Pharyngeal Sensitivity	1.93	0.25	<0.0001	6.9 (4.2-11.4)	410	393.1
5	Sedation, Anxiety	2.1	0.26	<0.0001	8.2 (5.0-13.5)	408.8	391.1
6	Sedation, Education: <High School	2.03	0.25	<0.0001	7.6 (4.7-12.5)	416.6	399
7	Sedation, Gender	2.02	0.25	<0.0001	7.5 (4.6-12.3)	419.2	401.6
8	Sedation, Age >55, Pharyngeal Sensitivity, Anxious, Positive Expectations	2.15	0.27	<0.0001	8.6 (5.0-14.6)	400.3	365.3
9	Sedation, Age (continuous), Pharyngeal Sensitivity, Anxious , Positive Expectations	2.19	0.28	<0.0001	8.9 (5.2-15.4)	397.9	363.1
10	Sedation, Age>55 , Pharyngeal Sensitivity, Anxious, Positive Expectations *rpharsens	2.46	0.33	<0.0001	11.7 (6.2-22.3)	402.5	361.7
11	Sedation, Age>55, Pharyngeal Sensitivity, Anxious, Positive Expectations, *ranxious	2.48	0.38	<0.0001	11.9 (5.6-25.2)	404.4	363.6
12	Sedation, Age>55, Pharyngeal Sensitivity Anxious, Positive Expectations, *rpositive expectations	2.36	0.5	<0.0001	10.6 (4.0-28.1)	405.8	365.1
13	Sedation, Age>55, Pharyngeal Sensitivity, Anxious, Positive Expectations, *rage>55	1.96	0.36	<0.0001	7.10 (3.5-14.5)	378.8	405.5
14	Sedation, Age>55, Pharyngeal Sensitivity Anxious, Positive Expectations, Smoker, *rsmoker	2.32	0.3	<0.0001	10.2 (5.66-18.4)	405.7	359.1
15	Sedation, Age>55, Pharyngeal Sensitivity Anxious, Positive Expectations, Prior EGD, *rprior	2.59	0.38	<0.0001	13.3 (6.3-28.2)	408	361.4
16	Sedation, Age>55, Pharyngeal Sensitivity Anxious, Positive Expectations, Staff Endoscopist, *rstaff	1.06	0.84	<0.0001	2.89 (0.55-15.08)	409.4	362.8

Legend:

*rstaff = interaction between sedation and staff endoscopist
*rsmoker= interaction between sedation and smoking status
*rprior= interaction between sedation and prior EGDE
*ranxious= interaction between sedation and anxious state
*rpharsens= interaction between sedation and pharyngeal sensitivity
*rpositive expectations= interaction between sedation and positive expectations
*rage55= interaction between sedation and age55

Appendix 2: Model Selection Process for Willingness to Repeat (Crude=3.84)

	Model	Beta Estimate for Sedation	Standard Error of Beta Estimate (Sedation)	P-Value	OR For Sedation (95% CI)	BIC	Log Likelihood Test
1	Sedation, Scope Time	1.3432	0.2598	<0.0001	3.83 (2.30-6.37)	404.91	387.3
2	Sedation, Scope Time, Gender	1.1462	0.267	<0.0001	4.12 (2.44-6.96)	395.16	371.7
3	Sedation, Scope Time, Gender, Dyspepsia	1.3766	0.2697	<0.0001	3.96 (2.34-6.72)	395.27	365.95
4	Sedation, Scope Time, Dyspepsia	1.2897	0.2621	<0.0001	3.63 (2.17-6.07)	404.49	381.01
5	Sedation, Scope Time, Elderly, relderly	1.3015	0.3086	<0.0001	3.68 (2.01-6.73)	415.88	386.56
6	Sedation, Scope Time, Age 55, rage 55	1.4638	0.3638	<0.0001	4.32 (2.12-8.81)	415.64	386.3
7	Sedation, Scope Time, Gender, rgender	2.0474	0.5157	<0.0001	7.75 (2.82-21.23)	398.5	369.18
8	Sedation, Scope Time, Smoker, rsmoker	1.4676	0.2884	<0.0001	4.34 (2.47-7.64)	412.3	382.98
9	Sedation, Scope Time, Gender, Dyspepsia, Elderly, elderly	1.3042	0.3181	<0.0001	3.66 (1.98-6.87)	405.96	364.93
10	Sedation, Scope Time, Gender, Dyspepsia, Age 55, rage 55	1.4457	0.3741	<0.0001	4.25 (2.04-8.84)	406.9	365.85
11	Sedation, Scope Time, Gender, Dyspepsia, Old Age, roldage	1.2989	0.2845	<0.0001	3.67 (2.10-6.40)	406.02	364.98
12	Sedation, Scope Time, Gender, Dyspepsia, rgender	1.3026	0.3355	<0.0001	7.16 (2.60-19.78)	398.96	363.78
13	Sedation, Scope Time, Gender, Dyspepsia, Smoker, rsmoker	1.5129	0.2992	<0.0001	4.54 (2.53-8.16)	403.32	362.29

Legend:

*rstaff = interaction between sedation and staff endoscopist
*rsmoker= interaction between sedation and smoking status
*rprior= interaction between sedation and prior EGDE
*ranxious= interaction between sedation and anxious state
*rpharsens= interaction between sedation and pharyngeal sensitivity
*rpositive expectations= interaction between sedation and positive expectations
*rage55= interaction between sedation and age55

Appendix 3: Model Selection Process Patient Satisfaction Alone (crude=9.53)

	Model	Beta Estimate for Sedation	Standard Error of Beta Estimate (Sedation)	P-Value	OR For Sedation (95% CI)	BIC	Log Likelihood Test
1	Sedation	2.2545	0.3771	<0.0001	9.53 (4.55-19.96)	309.58	297.8
2	Sedation, Gender	2.3088	0.3811	<0.0001	10.06 (4.77-21.24)	307.17	289.52
3	Sedation, Positive Expectations	2.2334	0.3812	<0.0001	9.33 (4.42-19.70)	304.58	286.96
4	Sedation, Gender, Positive Expectations	2.2868	0.3847	<0.0001	9.84 (4.63-20.92)	304.2	280.71
5	Sedation, Gender, Positive Expectations, Staff, rstaff	1.6588	1.165	0.1545	5.25 (0.54-51.53)	315.63	280.4
6	Sedation, Gender, Positive Expectations, Pharyngeal Sensitivity, rpharsens	2.6153	0.5035	<0.0001	13.67 (5.10-36.67)	304.53	269.54
7	Sedation, Gender, Positive Expectations, Staff, rstaff Pharyngeal Sensitivity, rpharsens	2.1246	1.2608	0.092	8.37 (0.71-99.06)	315.93	269.27
8	Sedation, Smoker	2.2209	0.3787	<0.0001	9.22 (4.39-19.36)	309.31	291.67
9	Sedation, Educational Status: <High School	2.2708	0.3791	<0.0001	9.69 (4.61-20.37)	307.47	289.84
10	Sedation, Pharyngeal Sensitivity, rpharsens	2.5777	0.4945	<0.0001	13.17 (5.00-34.70)	310.21	286.83
11	Sedation, Positive Expectations, Staff, rstaff	1.8373	1.1583	0.1127	6.28 (0.65-60.80)	316.21	286.83
12	Sedation, Gender, Staff, rstaff	1.7596	1.1593	0.1291	5.81 (0.60-56.36)	318.7	289.3
13	Sedation, Gender, Pharyngeal Sensitivity, rpharsens	2.6377	0.4987	<0.0001	13.98 (5.26-37.16)	307.72	278.51
14	Sedation, Positive Expectations, Pharyngeal Sensitivity, rpharsens	2.5582	0.4999	<0.0001	12.91 (4.85-34.40)	304.83	275.65
15	Sedation, Staff, rstaff	1.9459	1.1495	0.0905	7.00 (0.74-66.62)	321.25	297.71

Legend:

*rstaff = interaction between sedation and staff endoscopist
*rsmoker= interaction between sedation and smoking status
*rprior= interaction between sedation and prior EGDE
*ranxious= interaction between sedation and anxious state
*rpharsens= interaction between sedation and pharyngeal sensitivity
*rpositive expectations= interaction between sedation and positive expectations
*rage55= interaction between sedation and age55

Appendix 4: Model Selection Process for Doctor Satisfaction Alone (Crude=4.95)

	Model	Beta Estimate for Sedation	Standard Error for Beta Estimate of Sedation	P-Value	OR For Sedation (95% CI)	BIC	Log Likelihood Test
1	Sedation	1.5999	0.3233	<0.0001	4.95 (2.63-9.33)	325.53	313.76
2	Sedation, Pharyngeal Sensitivity	1.5043	0.327	<0.0001	4.50 (2.37-8.54)	318.92	304.32
3	Sedation, Pharyngeal Sensitivity, Scope Time	1.5098	0.3291	<0.0001	4.53 (2.38-8.63)	319.97	296.59
4	Sedation, Pharyngeal Sensitivity, Scope Time, rscopetime	0.7813	0.4692	0.0959	2.18 (0.87-5.48)	321.9	292.67
5	Sedation, Pharyngeal Sensitivity, Scope Time, Gender, rgender	0.7482	0.4156	0.0718	2.11 (0.94-4.77)	323.61	288.57
6	Sedation, Pharyngeal Sensitivity, Gender, rgender	0.7614	0.4125	0.0649	2.14 (0.95-4.81)	322.56	293.36

Legend:

*rstaff = interaction between sedation and staff endoscopist

*rsmoker= interaction between sedation and smoking status

*rprior= interaction between sedation and prior EGDE

*ranxious= interaction between sedation and anxious state

*rpharsens= interaction between sedation and pharyngeal sensitivity

*rpositive expectations= interaction between sedation and positive expectations

*rage55= interaction between sedation and age55

Questionnaire I

Initials:_____ No._____

Date:_____

(Check where appropriate and fill in the blanks)

_____In-patient or _____Out-patient

Demographics

Age:_____years Gender: M / F (circle)

Educational Level

_____Less than High School
_____High School
_____College (C.E.G.E.P.)
_____University

Race: (describe where your original roots are from)

___ White
___Black
___Other: _____
fill in if necessary

____Smoker / ____Nonsmoker

Do you have any allergies to medication?_____. If yes, to which medication:_____
_____

(Circle the most appropriate)

Are you an anxious person? Yes / No

Have you been treated for an anxiety disorder? Yes / No

-Do you take sleeping pills (ex. Dalmane, Imovane, Serax etc.) ? Yes/ No
-Do you take pills for anxiety or to relax (ex. Valium, Ativan, etc)? Yes / No
-Do you take painkillers (ex. Codeine, Empracet, Demerol, etc.) ? Yes / No

List the medication you are currently taking:

1._____ 5._____
2._____ 6._____
3._____ 7._____
4._____ 8._____

This questionnaire is designed to help your doctor to know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take to long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense or "wound up" :
    a) most of the time
    b) a lot of the time
    c) from time to time, occasionally
    d) not at all

2. I still enjoy the things I used to enjoy:
    a) definitely as much
    b) not quite as much
    c) only a little
    d) hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:
    a) very definitely and quite badly
    b) yes, but not too badly
    c) a little, but it doesn't worry me
    d) not at all

4. I can laugh and see the funny side of things:
    a) as much as I always could
    b) not quite so much now
    c) definitely not so much now
    d) not at all

5. Worrying thoughts go through my mind:
    a) a great deal of the time
    b) a lot of the time
    c) from time to time but not too often
    d) only occasionally

6. I feel cheerful:
   a) not at all
   b) not often
   c) sometimes
   d) most of the time

7. I can sit at ease and feel relaxed:
   a) definitely
   b) usually
   c) not often
   d) not at all

8. I feel as if I am slowed down:
   a) nearly all the time
   b) very often
   c) sometimes
   d) not at all

9. I get a sort of frightened feeling like "butterflies" in the stomach:
   a) not at all
   b) occasionally
   c) quite often
   d) very often

10. I have lost interest in my appearance:
   a) definitely
   b) I don't take so much care as I should
   c) I may not take quite as much care
   d) I take just as much care as ever

11. I feel restless as if I have to be on the move:
   a) very much indeed
   b) quite a lot
   c) not very much
   d) not at all

12. I look forward with enjoyment to things:
   a) as much as ever I did
   b) rather less than I used to
   c) definitely less than I used to
   d) hardly at all

13. I get sudden feelings of panic:
    a) very often indeed
    b) quite often
    c) not very often
    d) not at all

14. I can enjoy a good book or radio or TV program:
    a) often
    b) sometimes
    c) not often
    d) very seldom

15. Have you had any operations in the past? Yes / No
If yes, what operation(s) ?

1._____ 5._____
2._____ 6._____
3._____ 7._____
4._____ 8._____

16. Do you tolerate dental procedures well (circle)? Yes / No

17. How well do you tolerate pain? (circle one)

Well				Poorly
1	2	3	4	5

18. Has anyone in your family ever been diagnosed with stomach or intestinal cancer (circle)? Yes / No

19. What is the reason for you having this gastroscopy? Please circle yes or no for <u>each</u> reason described below.
(You may answer "yes" to more than one choice)

Heartburn	Yes / No
Vomiting	Yes / No
Ulcer	Yes / No
Indigestion	Yes / No
Swallowing Difficulty	Yes / No
Other:_____	Yes / No

20. Have you ever undergone gastroscopy before (circle)? Yes / No

21. If you have had a gastroscopy in the past were you given a sedative (i.e. intravenous medication given to relax you such as demerol, valium, etc) for the procedure (circle one answer)?
a) Yes, I have only had gastroscopy with sedation
b) No, I have only had gastroscopy without sedation
c) I have had some gastroscopies, I have tried at least once with sedation and at least once without sedation.
d) I don't know

If you have never had a gastroscopy please go directly to question 23.

22. How would you describe your prior gastroscopy experience? (circle one number)

Acceptable				Unacceptable
1	2	3	4	5

23. Has anyone you know ever had a gastroscopy(circle)? Yes / No

If you do not know anyone who has had a gastroscopy skip questions 24 and 25 and go directly to question 26.

24. If so, did they have sedation for the procedure(circle)? Yes / No / I don't know

25. How did they describe their experience? (circle one)

Acceptable				Unacceptable
1	2	3	4	5

26. What do you expect your experience to be? (circle one number)

Acceptable				Unacceptable
1	2	3	4	5

Questionnaire II- Physician's Evaluation

Initials:_____ No: 2_____

Date of assessment: _____/_____/_____
Year Month Day

Blood pressure:_____ Heart rate:_____ Respiratory rate: _____

Procedure

Endoscopist (name):_____

Endoscopy nurse present: Yes / No

Experience of endoscopist (circle one): -GI Staff -R1(GI) -R2(GI) -R3(GI) -Gen. Surg. Res. -Other:_____

Study nurse present? Yes / No

Indication for procedure:_____

Pharyngeal Sensitivity to anesthetic nebulizer:

Not sensitive				Extremely sensitive
1	2	3	4	5

Type of anesthetic nebuliser used (check one): _____Xylocaine or _____Tetracaine

Number of metered doses of anesthetic nebulizer:_____metered doses at _____mg per metered dose

Size of endoscope used (circle): Pediatric Regular Jumbo(therapeutic)

Adequacy of Procedure

Were these areas properly visualized?

Esophagus	Yes / No
Stomach	Yes / No
Retroflexion	Yes / No
Duodenum	Yes / No

Abnormal anatomy? Yes /No If yes, specify:_____

Procedure complications? Yes / No If yes, specify:_____

Biopsy done? Yes / No

Any other procedures? Yes / No If yes, specify:_____

Examiner's Opinion of Patient's Tolerance

Circle the number that, in your opinion, best describes the patient's tolerance

Acceptable				Unacceptable
1	2	3	4	5

Total time of procedure: _____min. _____sec.
(**Total time of procedure** defined as being the time from which the scope goes beyond the incisor teeth until the end of the diagnostic gastroscopy)

Total time in endoscopy room: _____min. _____sec.
(**Total time in endoscopy room** defined as being the time from which the physician enters the endoscopy room until the time the patient leaves the room)

Satisfaction of Endoscopist
The endoscopist is asked to evaluate the technical adequacy of the procedure

Totally Unsatisfied				Totally Satisfied
1	2	3	4	5

Study Preparation Given
-What type of study preparation (medication or placebo) was used and what dosage (***in mL***)?

Demerol:_____mL Versed:_____mL Other:_____:_____mL

Additionnal Medication Given
-In addition to the study preparation (medication or placebo) recorded above, were sedatives needed? Yes / No
If Yes, fill out below (***in mg, unlike the previous question***):

Demerol:_____mg Versed:_____mg Other:_____:_____mg

In the endoscopist's opinion, did the patient receive sedation? Yes / No

*******Satisfaction of Patient (as soon as possible after the gastroscopy: *PATIENT STILL BLINDED*)**
Rate the level of comfort you experienced during your gastroscopy (circle the number that best describes your choice)

Acceptable				Unacceptable
1	2	3	4	5

Satisfaction of Patient (at moment of discharge: *PATIENT NOW UNBLINDED*)
Now that you know whether you have received the real sedatives or the placebos, rate the level of comfort you experienced during your gastroscopy (circle the number that best describes your choice)

Acceptable				Unacceptable
1	2	3	4	5

Questionnaire 2: Patient's Evaluation (24 hour recall)

How was the gastroscopy?
Rate the level of comfort you experienced during your gastroscopy (circle on number that best describes your choice)

Acceptable				Unacceptable
1	2	3	4	5

Recollection of Procedure
How well do you remember your gastroscopy?

Not at all				Very well
1	2	3	4	5

If required, would you undergo this procedure under similar conditions again? Yes / No