NEUROPSYCHOLOGICAL RECOVERY AFTER MIDAZOLAM COINDUCED GENERAL ANESTHESIA

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NEUROPSYCHOLOGICAL RECOVERY

AFTER MIDAZOLAM COINDUCED GENERAL ANESTHESIA

By

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ABSTRACT

INTRODUCTION: Following ambulatory surgery, rapid return of cognitive function is imperative. Data on the recovery of cognitive function after low dose midazolam coinduced general anesthesia is limited. It is unknown if coinduced general anesthesia allows faster return of function due to lower total drug dosages or prolongs cognitive recovery due to benzodiazepine effects. This study uses neuropsychological testing to measure cognitive recovery after midazolam coinduced anesthesia compared to propofol induced controls in ambulatory gynecology patients undergoing short laparoscopic procedures.

METHODS: With approval of the hospital research ethics board, 88 eligible patients were randomized in a double blind manner into one of two groups; propofol 2mg/kg control (n=44) or midazolam 0.02mg/kg with propofol 1mg/kg coinduced group (n=44). All patients received a standardized general anesthetic including endotracheal intubation. Neuropsychological objective testing consisted of a Digit Symbol Substitution Test (DSST), a Trieger Dot Test (TDT) and five Visual Analogue Scales (VAS) for subjective assessment of anxiety, sedation, coordination, confusion and drowsiness. Tests were completed preoperatively and postoperatively every 30 minutes until discharged. Intraoperative variables (including adverse events, hemodynamics), time to discharge, Post Anesthesia Care Unit (PACU) narcotic and anti-emetic use were recorded.

RESULTS: At 60 minutes postoperatively, 84 of the 88 subjects had complete data sets. Statistical significance was not reached (all ρ's >0.05) on tests of postoperative neuropsychological recovery comparing the propofol control group and the midazolam coinduced group. The groups had clinically similar scores on the VAS testing, DSST (51.8+/-12.7 vs. 55.7+/- 10.5 ρ=0.12, 95%CI –9.01 to 1.11 to detect a difference of 13.8) and TDT (7.9+/-7.3 vs. 7.1+/- 5.8 ρ=0.56). The DSST, TDT and VAS data were further analyzed using repeated measures ANCOVA to compare groups over time (with baseline preoperative test scores as covariate) and no significant difference (DSST ρ = 0.78) was found based upon group randomization. There was no significant difference in intraoperative hemodynamic parameters, the incidence of adverse events (3(7.1%) vs. 2(4.8%)); failed induction (5(11.9%) vs. 5(11.9%)); length of PACU stay (1:31+/-37 vs. 1:23+/-32 min); PACU morphine (0.13+/-0.10 vs. 0.13+/-0.11mg/kg); ondansetron rescue (13(31%) vs. 12(28.6%)). There was no intraoperative awareness in either group.

DISCUSSION: Midazolam in a low dose (0.02mg/kg) used as a component of coinduced general anesthesia for short ambulatory procedures does not appear to alter cognitive recovery as measured by neuropsychological testing compared to standard propofol (2mg/kg) induction. Intraoperative and PACU variables also appear to be similar between techniques. Thus, there is no disadvantage in recovery characteristics nor does there appear to be any advantage or disadvantage with respect to hemodynamic stability, quality of induction or drug cost. Due to rarity of intraoperative recall, we cannot conclude if midazolam is protective.

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CHAPTER 1

Introduction

SCIENTIFIC BACKGROUND

Intravenous Anesthetic Induction Agents

Intravenous anesthetic induction agents rapidly cause the loss of consciousness or the induction of hypnosis / sleep upon patients undergoing general anesthesia. These drugs are thought to potentiate the activity of the gamma-aminobutyric acid (GABA) at the GABA receptor in the central nervous system (1). This neurotransmitter is the principal inhibitory neurotransmitter within the central nervous system (CNS). The GABA receptor exists as a receptor complex (figure #1.1) - the GABA receptor, chloride ion channel, barbiturate binding site and a benzodiazepine binding site (1,2). When the GABA receptor is activated, the transmembrane chloride conductance increases which in turn results in hyperpolarization of the post-synaptic cell membrane. This results in functional inhibition of the post-synaptic neurone. The binding of an intravenous induction agent to its specific sub-unit within the GABA receptor complex will decrease the rate of dissociation of GABA from it's receptor, thereby increasing the duration of the GABA mediated opening of the chloride channels. The resulting inhibitory cell membrane hyperpolarization is presumed to be how these agents exert their sedative–hypnotic effects (2).

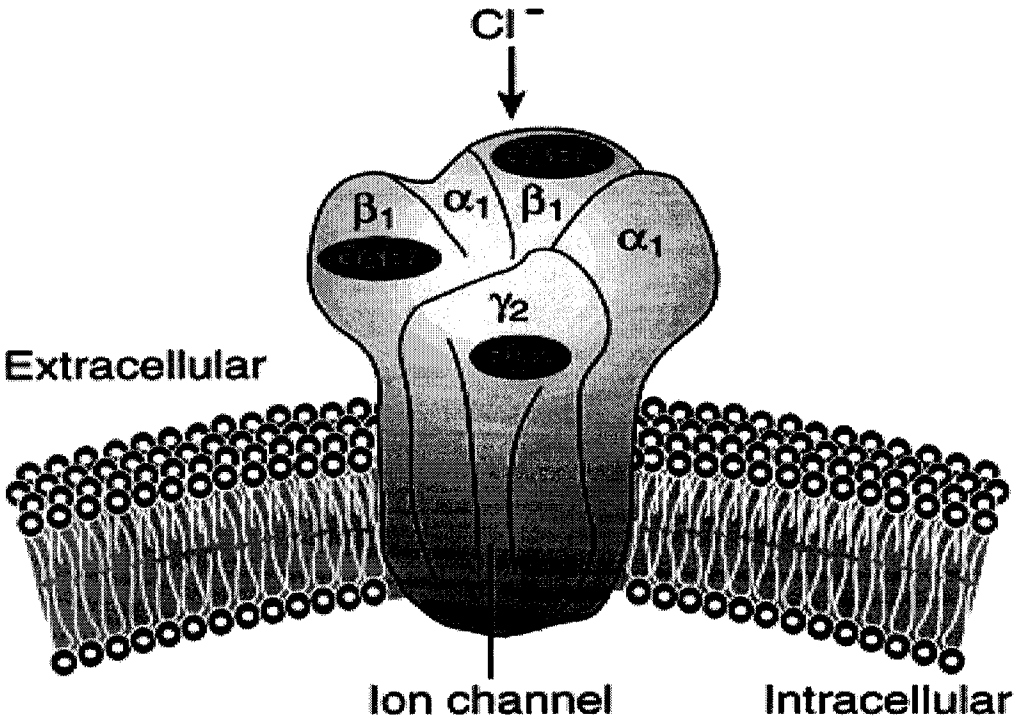


Figure # 1.1 GABA Receptor Complex – with receptor sub-units α / β / BDZ within the complex (BDZ = benzodiazepine)

The ideal intravenous induction agent needs to be potent, with rapid onset, relative short duration of action and have rapid, complete recovery even after prolonged administration. There should be little therapeutic variability i.e. predictable onset / offset of action. There should be minimal cardiovascular and respiratory depressant side effects. It should allow rapid recovery with minimal postoperative side effects such as nausea and vomiting, headache, prolonged sedation " hangover" or cognitive effects. There should be inactive non-toxic metabolites with metabolism and excretion independent of the liver and kidneys. Such agents must have a relative lack of side effects including minimal histamine release, allergic reactions, and alterations of intracranial pressure or teratogenic potential (1). The drug dose that is suggested for use in the induction of general anesthesia is the ED50 (3). The ED50 of an anesthetic induction agent is the *Estimated Dose* of that drug that will reliably induce hypnosis in *50%* of patients.

Several classes of anesthetic induction agents are used in clinical practice.

Barbiturates -	derivatives of barbituric acid i.e. methohexital, sodium thiopental, thiamylal, pentobarbital
Carboxylated imidazoles-	etomidate
Isopropophenols-	propofol
Phencyclidine derivatives-	ketamine
Progestrone derivatives-	eltanolone

First introduced into clinical practice in 1934, sodium thiopental (Pentothal®) is a thiobarbituarate derivative of barbituric acid (4). Thiopental was the first widely used

intravenous anesthetic induction agent and has been used almost exclusively for over 50 years. Thiopental is still accepted and used in clinical practice. Sodium thiopental was the historic gold standard to which all other newer intravenous induction agents are compared (1,4). Sodium thiopental is not an ideal intravenous anesthetic agent. New drugs, within the barbituric acid class as well as others have been developed and introduced into clinical practice in the past three decades. These new drugs strive to meet the ideal pharmacological criteria. Newer intravenous induction agents include ketamine (Ketalar®), methohexital (Brietal®), etomidate (Amidate®) and propofol (Diprivan®) (1,4).

Intravenous benzodiazepines such as diazepam and midazolam have been used as anesthetic induction agents. Benzodiazepines compared to standard intravenous induction agents (i.e. thiopental, propofol) are slow with respect to onset and are unpredictable due to wide variation in dose response relationship (1,4). Compared to other standard intravenous induction agents benzodiazepines have a prolonged recovery i.e. time to return to consciousness and time to orientation (1,4,5). Midazolam, a newer water soluble benzodiazepine is slightly more rapid in onset, with a shorter elimination half-life compared to older drugs such as diazepam. Midazolam 0.15-0.2mg/kg (ED50 for induction) was initially felt to be an acceptable induction agent. Compared to diazepam it had a more rapid onset and recovery but when compared to thiopental or propofol it was still inferior as an intravenous induction agent (4,5). Benzodiazepines therefore are not used routinely as intravenous anesthetic induction agents (1,4).

Propofol, the most recently introduced anesthetic induction agent is a novel intravenous induction agent not related to any other class of intravenous induction agent. Propofol was developed and introduced into clinical practice between 1986-1989. Propofol has gained acceptance and popularity in clinical practice during the past decade. The use of propofol now surpasses sodium thiopental, despite similar induction qualities and greater expense. Since its introduction, Astra–Zeneca, the proprietary owners of Diprivan® (propofol) estimates propofol has been used in over 330 million patients.

The supremacy of propofol over other induction agents including the barbiturates in part comes from its recovery characteristics. Propofol induced anesthesia recovery is associated with faster eye opening, faster time to discharge, improved cognitive function and less post-operative nausea and vomiting. Propofol therefore is felt to be a better intravenous induction agent for the ambulatory surgery patient (6-10). Propofol it is now considered the gold standard (4) to which all other agents are compared. Generic formulations of propofol now available have reduced cost allowing more routine use. Despite this propofol is not an ideal intravenous anesthetic agent. Propofol is still more expensive than thiopental, causes moderate pain on injection in a large proportion of patients, supports bacterial growth and may cause profound bradycardia / asystole on induction (4).

Unfortunately there is no ideal intravenous induction agent. The newer agents have incorporated some of the characteristics of the ideal agent but each fails in areas where other induction agents succeed. Depending upon the specific drug, the various

agents all have advantageous and deleterious pharmacological properties that may make them more or less desirable for a specific clinical situation. When deciding upon which agent to use, the anesthesiologist must consider these characteristics (1).

Drug Synergy

Synergistic drug interactions occur when the effect of a drug combination is greater than the sum of the individual components i.e. the effect is supra-additive (11). Interactions between biologically active agents are important, as the combined effect may offer therapeutic advantages over single agents (e.g. combination chemotherapy). Modern anesthetic techniques usually utilise these interactions using a "balanced anesthetic technique". This involves deliberate poly-pharmacy to maximise the desired drug effects and to minimise undesired drug effects. The term "coinduction" was first used to describe the unplanned induction of general anesthesia by non-anesthetic personnel providing sedation utilising benzodiazepines and narcotic agents in unsuitable environments (12).

Subsequent investigations using isobolographic analysis documented drug synergy when combining anesthetic agents (thiopental: morphine / propofol: fentanyl / thiopental: midazolam / propofol: midazolam / midazolam: alfentanil etc) both in animals and humans (13-21). Specific interest developed in evaluating "coinduction" or synergistic drug interactions for *induction agents* with narcotics and / or benzodiazepines.

Isobolographic analysis provides a precise means of measuring drug interactions.

On an isobole diagram (see figure #1.2), points on the X and Y axes (usually representing the potencies (ED50) of each of the two drugs when used alone) are joined by a straight line. This line defines the fractional combinations of the two agents that would be expected to have this same potency if the interaction between the two agents was additive. If the reference point (i.e. ED50 for anesthetic induction agents) of a combination of two agents falls significantly to the left of this additive straight line, a synergistic interaction between the two agents is inferred. If the interaction lies to the right above the straight line then a presumed drug antagonism occurs.

Isobologram

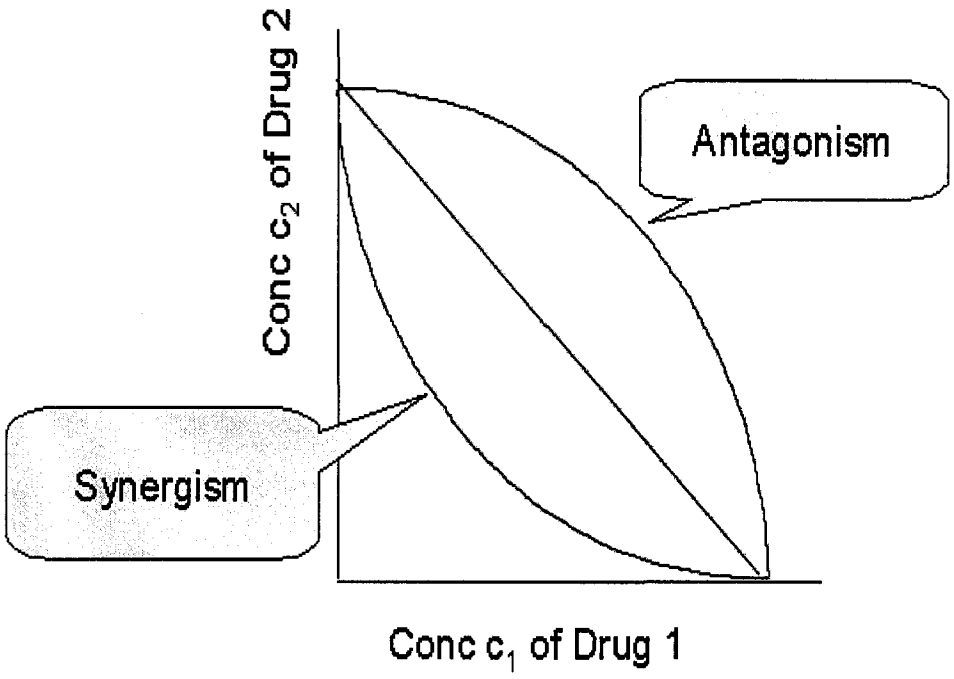
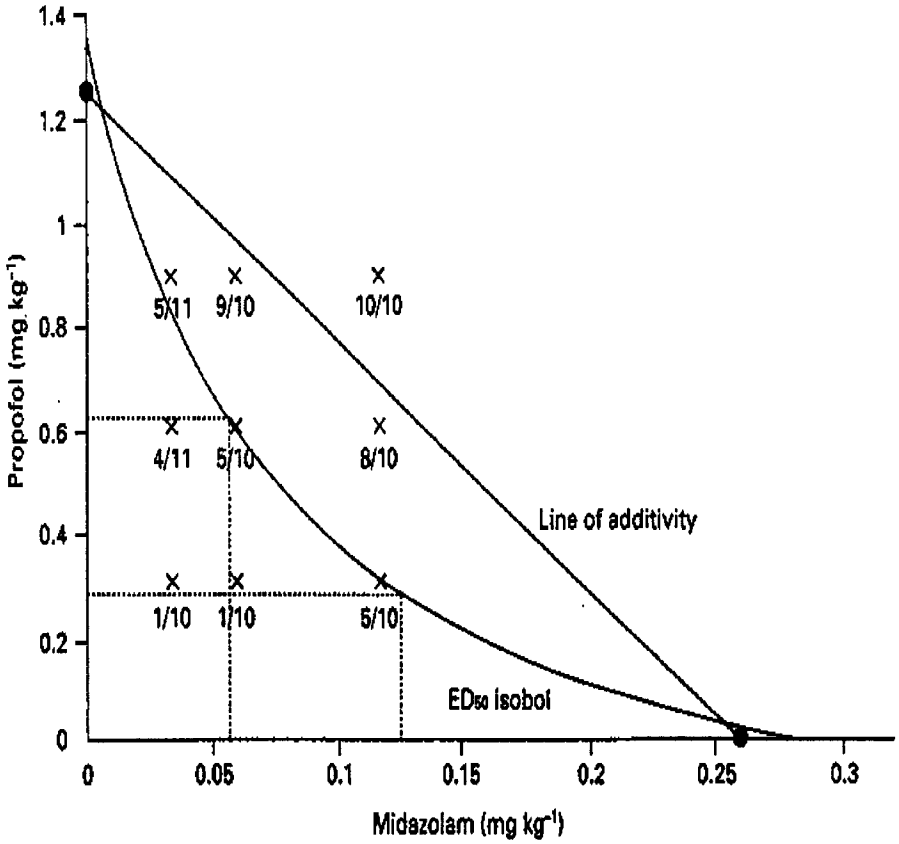


Figure #1.2 Isobologram of Drug Interactions. Additive drug interactions fall on the straight line. Synergy occurs if the drug effect lies to the left of the line and antagonistic interaction when it is to the right

Kissen et al (14) initially demonstrated a 75% dose reduction for midazolam and a 75% dose reduction for sodium thiopental when given in combination to rats. The biologic basis for this potentiation is thought to occur via the benzodiazepine sub-unit on the GABA receptor complex (18)(see figure #1.1). Various combinations of agents (thiopental, propofol, alfentanil, morphine, midazolam etc.) and the degree of drug synergy were studied and documented using isobolographic analysis (15,17,18,22-24).

Isobolographic analysis of midazolam and propofol indicates that there is drug synergy with the ED50s falling left of the line of additivity. There are various equipotent ED50 drug dosage combinations along the ED50 isobol that could be used to produce hypnosis comparable to propofol ED50 of 2mg/kg (see figure#1.3). Referring to figure #1.3, the dashed lines show two combinations, with the X and Y intercepts being the individual drug doses to be used in the combination.

MIDAZOLAM-PROPOFOL SYNERGISM



ED_{50} isobologram for midazolam-propofol combination as predicted by the probit interaction model (labelled ED_{50} isobol) for the clinical end-point, loss of response to command. The equation for this curve is: $6.86X+1.43Y+18.79XY-1.93=0$; where X and Y are the doses of midazolam and propofol, respectively. Successful induction rates for the nine drug combinations studied in phase 2 are shown. Midazolam-propofol combinations referred to in the text are denoted by dotted lines.

Figure#1.3 Isobolographic Analysis of Midazolam-Propofol. The diagram shows numerous possible synergistic combinations (McClune et al)[1]

[1] McClune,S., McKayA.C., et al Synergistic interaction between midazolam and propofol. British Journal of Anaesthesia 1992;69:240-245

Anesthetic Coinduction Technique

Taking advantage of drug synergy numerous studies in man have confirmed that *induction of general anesthesia* could be *reliably* accomplished using a much lower total drug dosage (14-24). The term "coinduction technique" was adopted for concurrent administration of two or more drugs utilising drug synergy to facilitate induction of general anesthesia. The combination of propofol and midazolam became one of the most commonly used "coinduction techniques". The synergistic drug effect allowed much smaller total drug dosages to be utilised during induction of general anesthesia, yet the same clinical end point of hypnosis was achieved.

As indicated by figure #1.3 there are various synergistic drug combinations for propofol and midazolam. Vinik (25,26) suggested using the combination of midazolam 0.02mg/kg (one-tenth the usual induction dose of midazolam 0.2mg/kg), which was to be injected two minutes before 1mg/kg propofol (one half the usual induction dose of propofol). This "coinduction technique" suggested by Vinik gained popularity in mid 1990's. This was in part due to strong marketing by Hoffman–LaRoche Ltd. who held the patent for midazolam (proprietary name-Versed®). It was also striving to achieve the "ideal" intravenous induction agent. Coinduction using synergistic drug interactions of propofol and midazolam was expounded as the latest "ideal" agent. The use of propofol and midazolam in a "coinduction technique" became the principal induction technique for ambulatory / day case patients. Numerous benefits of coinduction were hypothesised but few had been proven.

Proponents of the coinduction technique (25-29) proposed that there should be less cardiovascular depression with improved hemodynamic stability and less respiratory depression with lower total drug dosages. Possible other hypothesised benefits included faster recovery, time to eye opening and possible earlier discharge. The current move for health care cost containment made pharmacoeconomic savings due to smaller total dosages and possibility of earlier discharge attractive possible benefits of coinduction (29).

Improved Surgical Outcome

During the 1980's and early 1990's surgery underwent a revolutionary change (30). Introduction of minimally invasive techniques, newer approaches to postoperative pain management and focus on early mobilisation allowed more elective operations, including more extensive surgeries to be done on ambulatory patients. Advances in anesthetic techniques including development of rapid short acting volatile anesthetics, opioids and muscle relaxants facilitated this change.

More surgical patients were undergoing "ambulatory" procedures and discharged home after the surgical procedure. Further-more, patients undergoing short, minor surgical procedures were being "fast tracked" - discharged 30 minutes post general anesthesia without going to a post anesthesia care unit (PACU). Ultimately, more patients are going home, going home earlier, and going home after much larger surgeries. This philosophic change in health care delivery and in perioperative care was felt to be an

improvement in overall surgical outcome and patient care (6). This trend was fuelled also by increasing health care costs and the efforts of health care managers to contain them. There were definite economic benefits to operating room budgets with fewer hospital admissions, earlier discharge and "fast tracking". There was a definite need for ambulatory patients to be "discharge ready" and "street ready" as early as possible.

Optimization of anesthetic technique and especially the recovery characteristics of general anesthetics became more important to anesthesiologists and health-care managers. Ultra short acting drugs were developed and marketed for general anesthesia in ambulatory patients. The recovery characteristics of anesthetic induction agents now became as important as the induction qualities. Many studies looked at the recovery characteristics of the various intravenous induction agents i.e. sodium thiopental, methohexital, propofol, diazepam, midazolam etc. (5,7,8, 31-38).

Anesthesia Recovery

The recovery period or time after administration of general anesthesia is broken down into several time intervals. Early recovery may be defined as the time interval when patients emerge from anesthesia, are recovering protective reflexes and motor activity. This may be a period of altered physiologic function and hemodynamic instability. Intermediate recovery is the period when level of consciousness, co-ordination and physiologic function has normalised. Late recovery therefore is when the patient is fully back to preoperative function and has return of normal behaviour or cognitive function.

Early stages of recovery after general anesthesia can be assessed by one of two ways. First, by noting the time that *fixed events* occur i.e. time to eye opening, time to extubation, time to obey commands and / or time to discharge. Alternatively recovery may be evaluated at *fixed times* using a scoring type system i.e. the Glasgow Coma Scale, the Aldrete-Kroulik Post Anesthetic Recovery Score or the Stewart Score (39). The Aldrete Score introduced in 1970, is a commonly used score during admission to Post Anesthesia Care Units (PACU) to assess physiological function. This and other scoring systems were designed to convey objective information about the physical condition of patients admitted to PACU after an anesthetic. The Aldrete Score evaluates level of consciousness, activity, respiration, circulation and colour (40). This scoring system conveys information about physiologic stability and its return to preoperative levels or baseline. It was and still is used primarily as a guide for early recovery and transfer from PACU to the in-patient ward. It does not provide information about late recovery.

Late recovery assessment conveys information about residual drug effect on cognitive function and assesses ability to return to real life tasks. Subjective assessment of late recovery maybe made by the patient or the PACU nursing staff but objective assessment using neuropsychological testing may be more sensitive to residual anesthetic effects on cognitive function (these residual effects may actually reduce patients' insight into their own mental impairment)(39).

Neuropsychological testing (41) may serve as surrogate markers to assess the recovery of these functions. Neuropsychological tests are objective assessments made on

various aspects of psychomotor function using "idealised tasks" such as "reaction time" (as opposed to "real tasks" such as "driving an automobile"). Neuropsychological tests have been adapted or modified from the psychology literature where they are used to test intelligence. The results are then interpreted using psychological models of cognitive / psychomotor function (39).

Cognition or psychomotor function is multidimensional encompassing areas such as sensory input processing, motor function, central processing, vigilance, and memory. Different sub-tests measure different aspects of psychomotor function. Performance on neuropsychological tests and exact clinical significance and correlation with decision making or "street readiness" is still ambiguous. Generalisation about street fitness and return to baseline measure must be made with caution (39,64). It may not be possible to measure or assess complex human behaviour especially around "decision making processes" but these idealised tasks are likely the best assessment tool or surrogate makers of it.

Discharge Assessment

Discharge from PACU may be to the inpatient ward or as in ambulatory surgery to home. Assessment for discharge from PACU occurs somewhere between intermediate and late recovery. Criteria used to transfer a patient to the ward cannot be used alone in ambulatory patients to determine "home readiness" (42). Ambulatory patients who are "home ready" are clinically stable, have recovery of basic cognitive function and have

regained the ability to walk, void and maintain adequate oral intake and pain control. This is a much higher standard compared to inpatient discharge.

"Street readiness" after anesthesia likely includes the ability to return to complex tasks such as crossing a street, using public transportation unaccompanied or driving. It is difficult to determine exactly when complete recovery of these complex cognitive functions occurs. The ability to sign legal documents according to Canadian Anesthesiologist's Society guidelines[2] is no earlier than 24 hours post anesthesia

Neuropsychological Tests of Cognitive Recovery

When considering which test to use to measure cognitive recovery, several factors need to be assessed. Ideally in clinical practice these tests must be quick and simple to administer, have no learning effect, can be used by an unskilled operator and require inexpensive equipment. The tests should be validated in the post general anesthetic population. Late recovery or assessment of cognitive recovery utilising neuropsychological testing is used in the anesthesia research / literature. These neuropsychological tests maybe complex, time consuming and may require standardised administration. These tests and therefore assessment of late recovery are not routinely used in clinical practice.

[2] Guidelines to the Practice of Anesthesia as recommended by the Canadian Anesthesiologist's Society. Toronto Canada 2003

Benzodiazepines and Cognitive Function

Benzodiazepines are classed as sedative–hypnotics (oral sleeping pills / anxiolytics). They are true amnestics in that they can produce amnesia without sedation. Most anesthetic agents may produce amnesia only if they are sufficiently sedating. Benzodiazepines have been documented to have impairment or "hangover" effects on cognitive function extending after the sedative effect has gone (43). These undesirable effects impair learning, memory and psychomotor functions (43,44). This can be more pronounced in geriatric patients (45). As earlier indicated midazolam for general anesthesia induction has been shown to prolong standard recovery assessments. Midazolam as a preoperative sedative have conflicting reports on its effect on recovery (46,47). Concerns about potency and the residual effects of intravenous midazolam increased in 1988 after 57 reports during a 2 year period to the FDA involving 30 deaths with midazolam conscious sedation (48). This correlated clinically to what other local health care providers (personal communication) were observing when midazolam was used for procedural conscious sedation. The patients look awake and respond appropriately during post procedure conversation. They appeared suitable to discharge home, however on follow up patients would often have no recollection of the conversation. The patients did not recall post procedural instruction or restrictions and/or test results. The potential and duration for post procedure respiratory depression did have catastrophic consequences. The duration of post procedure amnesia was uncertain and a second area of risk in ambulatory patients. Retrograde and anterograde amnesia after

benzodiazepines administration may be desired *during* and *before* general anesthesia, anterograde amnesia certainly is undesirable *after* general anesthesia is complete. This is particularly true in the ambulatory anesthesia patients who are discharged home, appear to be back to preoperative function but in actual fact may have no recollection of the first few hours after their discharge.

Midazolam Coinduction and Recovery

Given this background information i.e. effects of benzodiazepines on cognition, need for fast recovery and early discharge, the effect on recovery of a coinduction technique within the context of ambulatory anesthesia was questioned. Was there need for concern using a very low dose benzodiazepine -one-tenth the ED50 for induction or one-fifth to one half conscious sedation doses? It was unclear as to what would happen to the recovery characteristics after a midazolam coinduction technique. The risk / benefits of adding a low dose benzodiazepine during a coinduction technique was questioned in many operating room lounges and anesthesia society meetings. Would it indeed speed up time to eye opening and possible time to discharge due to lower over all drug administration or cognitively impair patients due to the benzodiazepine effect possibly making discharge especially early discharge unsafe? Could the addition of a benzodiazepine with documented anterograde amnesia be protective against intra-operative recall? The answers to these questions were not readily apparent.

LITERATURE REVIEW

A primary literature review was conducted initially in 1996 using the National Library of Medicine MEDLINE (Silver Platter CD-ROM version initially and then WinSpirs). In early 1997 the search was updated and conducted via Grateful Med (Internet version). Initially we were interested in finding trials similar to our own practice using midazolam propofol coinduction and cognitive recovery characteristics. The database back to 1966 was searched using midazolam, coinduction, cognition, neuropsychological recovery, discharge, and general anesthesia (see Appendix A). As this was a relatively new technique these searches revealed very little published data on midazolam coinduction and even less on recovery characteristics. We broadened our search to retrieve general studies of coinduction using alternative anesthetic agents, drug synergy including midazolam, and any reports on midazolam coinduction techniques. These searches revealed numerous articles documenting drug synergy utilising various agents including midazolam, midazolam as an intravenous induction agent, but only three articles noting recovery characteristics after midazolam coinduced general anesthesia (328,29,49).

These consisted of two abstracts and one publication, which were retrieved. A secondary search of any applicable references within these articles was hand reviewed and retrieved. The secondary search also included a Science Citation Index search. This was conducted to find any further publications that had subsequently cited these articles and had not initially been found. If necessary, personal communication with the authors

was attempted for clarification about methodology or if unanswered questions remained. This yielded the full text article of one of one the initial abstracts retrieved.

The three articles that appeared to be applicable are as follows. Delucia et al (27) published an abstract in 1992 titled "Effect of Midazolam on Induction and Recovery Characteristics of Propofol" describing results of a randomised control trial of 75 patients undergoing brief general anesthesia using placebo, low or high dose midazolam along with propofol for induction. This study was designed to evaluate perioperative effects of intravenous midazolam when administered as an adjuvant to propofol for coinduction of outpatient anesthesia. The assessment of recovery found a statistically significant prolongation of awakening and time to extubation and time to orientation in the high dose midazolam group but not in the low dose midazolam group. Neuropsychological tests or further cognitive assessments were not completed. Despite contacting the research supervisor (co-author) no subsequent publication of these data in full article format could be found and appears was not completed.

Elwood et al (28) published in 1995 a randomised control trial of 64 patients undergoing short elective procedures with general anesthesia. Patients were randomised to receive placebo, low or high dose midazolam along with propofol for coinduction. Time to eye opening and time to discharge were used to assess recovery characteristics. A statistically significant delay in time to eye opening was found, with no difference in time to discharge (Power 80% to find 39-min. delay). No neuropsychological assessments of cognitive recovery were done.

Work by Miller et al (49) in 1995 abstract and the full article published 1996 evaluated the synergistic drug effects of midazolam on propofol requirements and recovery quality of this combination used during a total intravenous anesthetic (TIVA) technique. The primary outcome of this study was the effect of graded doses of midazolam on propofol induction requirements and on maintenance infusion rates. The effect on recovery times including assessment of cognitive function and patient satisfaction were secondary outcomes. Recovery was assessed by time to awakening, time to discharge and score on "psychometric" (neuropsychological) testing (Trieger Dot Test).

A TIVA technique does not use inhalation / volatile vapour anesthetic for anesthesia maintenance. TIVA uses an intravenous infusion of an anesthetic agent using volumetric infusion pump for maintenance of anesthesia. TIVA general anesthesia is not the standard technique for general anesthesia administration. Midazolam, as expected with drug synergy, in this study reduced the induction requirements but surprisingly not the maintenance requirements of propofol for TIVA (49,50). Compared to standard inhalation anesthesia for maintenance, there is a much larger total drug dosage of propofol used for the TIVA anesthetic. These two anesthetic techniques may differ in terms of recovery qualities and benzodiazepine effects of them. It may not be valid to extrapolate these results from a study of total intravenous anesthesia to a setting with coinduced inhalation general anesthesia.

A sample size of 100 subjects was used but details of sample size estimation were

not included. Ninety of 100 ambulatory patients undergoing short surgical procedures were randomised into 4 groups to receive placebo or one of three midazolam dosages. This study was discontinued before the complete sample size was attained, as an unexpected high incidence of intraoperative awareness was encountered with the TIVA technique. Despite this data analysis was completed and no statistically significant differences were found in either of the recovery assessments including the TDT over time for the four treatment groups (Kruskal-Wallis α=0.05).

This study, which was halted because of an unusually high incidence (6.7%) of intraoperative awareness which was felt to be as a result of inadequate anesthesia with the TIVA technique (spontaneous reporting of awareness is reported Lui (51) to be 0.1 – 0.2% of all general anesthetics). It is of interest that the 4 of the six subjects who experienced intraoperative recall were in the placebo group, one of the six in the low dose midazolam group. The rate of intraoperative recall between the groups did reach statistical significance. It is noted that the midazolam group of patients while requiring less induction drug received similar propofol maintenance infusion rates as the placebo group. The authors postulated that midazolam from anterograde amnesia may afford a protective effect on intraoperative recall. The authors suggested that midazolam should be added to TIVA techniques.

The data from all these studies provided some evidence that midazolam in high dose coinduction techniques but not low dose techniques may delay early markers of recovery such as time to eye opening, time to awakening and extubation. This however

did not delay discharge time. The studies using low dose midazolam had equivocal effects on either early recovery characteristics but again did not delay discharge.

It was apparent that insufficient evidence existed to determine if midazolam coinduction impaired neuropsychological markers of cognitive recovery post general anesthesia. As previously stated, recovery of cognitive function is subtle to assess post general anesthesia and likely is not assessed using routine markers of physiological recovery. While there are some publications that attempt to address the effect of midazolam coinduction on cognitive recovery, we felt that these assessments were not valid measures of complex cognitive function. We wished to have a more precise validated assessment of the cognition, which may or may not be more relevant to clinical recovery of higher cognitive function or if possible assess "street readiness" after general anesthesia.

Hence, the rationale leading to a well designed, randomised control trial to determine whether there is a significant treatment effect of midazolam coinduction on cognitive function as measured by neuropsychological tests. Secondary outcomes were to look at various intraoperative parameters such as induction characteristics i.e. reliability, hemodynamic stability, adverse events and overall induction agent drug cost. Postoperative variables to be assessed included narcotic and anti-emetic requirements, Aldrete score, time to discharge and intraoperative recall.

STUDY OBJECTIVE

The goal of this study is to determine whether midazolam given in low doses during coinduced general anesthesia adversely affects or slows cognitive recovery by comparison of those subjects who receive this benzodiazepine as part of the general anesthetic induction to those who do not.

RESEARCH QUESTION

In ambulatory gynaecologic patients undergoing elective laparoscopic procedures of short duration (30 to 90 minutes), is there a clinically important difference in cognitive function on neuropsychological testing during recovery as measured by the Digit Symbol Substitution Test in patients receiving midazolam coinduced general anesthesia compared to standard propofol induction of general anesthesia?

CHAPTER 2

Research Design and Methods

RESEARCH DESIGN

This clinical trial was a prospective, randomised, double blinded study.

Blinding

Patients enrolled in the study were not aware to which treatment group they were randomised and which drugs they received. The investigator performing the outcome assessments was not aware of the patients' treatment group. It is hoped that bias on the part of the investigator or the patient will be minimised by this endpoint blinding.

The attending anesthesiologist administering the general anesthetic was not blinded. After randomization, the anesthesiologist was given the treatment assignment in an envelope. The envelope contained a card noting the study number and treatment assignment. The envelope on the exterior indicated drug dosages for both study groups based upon the patient's weight. Only the study number was documented on the anesthetic record. The total drug dosages that were administered was recorded on the card and placed inside the envelope. The card was sealed in the envelope and attached to the to the consent form and anesthetic record on the patients chart. This allowed safety in administration of study drugs, blinding of the anesthetic record as well as immediate ability to unblind the study drugs if an adverse reaction occurred. This is done without compromise to the study integrity, as the attending anesthesiologist did not complete any

of the outcome assessments.

The attending anesthesiologist and operating room nurses were reminded prior to start of each study case that the drugs administered were not to be revealed to either the patient, PACU staff or the outcome assessor. The induction drugs were drawn up between surgical cases (only cleaning staffs were present). The surgical team was blinded, as they were not in the operating room during anesthetic induction. It is possible that nursing / scrub staff who were present during administration of induction drugs may have been able to identify the drugs administered and therefore aware of group assignment.

The outcome assessor and PACU staff only had access to the patient's blinded anesthetic record. Subsequent to the outcome assessment and grading, the group assignment was then unblinded by opening the sealed envelope. The group assignment and drug dosages administered were then noted on the data collection record.

Randomization

Subjects were randomised by blocked, stratified randomization to either

Group A propofol 2mg /kg or

Group B midazolam 0.02mg/kg : propofol 1mg/kg.

using a sealed envelope system.

Variable blocking of randomization was utilized. The size of the block was determined empirically as an even number chosen from 6 to 20 to a total of 88 subjects.

Stratification for age was carried out for each randomization group. The

definition of elderly, while arbitrary is usually age greater the 65 years (52). Healthy elderly patients exhibit normal physiologic change associated with ageing. These changes include physiologic reduction in organ function and altered redistribution kinetics (1,52,53). This, in addition to chronic disease co-morbidity and poly-pharmacy, influences the pharmacokinetic and pharmacodynamic properties of most therapeutic agents.

Elderly patients may require weeks to months to recover full preoperative mental status (54). In one study, 13% of elderly patients had some form of long term memory loss or "serious mental deterioration" after surgery (55). Age therefore is an important prognostic factor in cognitive recovery from general anesthesia. Increasing age has been shown to be a factor in prolonged duration of effects of benzodiazepines on cognitive function (52). The Wechsler Adult Intelligence Scale (WAIS) (56) manual has normalised sub-test scores for age. The norms table is subdivided into groups of 55–64 and 65–69 years of age. For these reasons age was stratified into two groups (younger than 65 years and 65 years and older) prior to group randomization.

Randomization Envelope Assembly

Randomization envelopes were assembled by a disinterested third party (departmental secretary). She would determine block size, then assign half of the block size to **Group A** -standard treatment and half to **Group B** -the intervention group on an index card. The cards were then shuffled and placed within opaque envelopes. The envelopes were sealed and shuffled a second time. The randomization number was then

written on the envelope exterior in order from 1 to 88. Randomization envelopes were placed sequentially in a box in the research office within the Department of Anesthesia. Randomization envelops where then removed from the box in correct numeric order. Once removed from the box, the randomization envelope, along with the patient data collection record and consent form, was placed on the patient's chart to accompany the patient into the operating room.

Allocation of treatment was therefore due to chance with important characteristics such as weight, ASA class, or length of surgery also being distributed equally by chance. Randomization also tends to equally distribute unrecognized confounding factors in the long run. Despite proper randomization, chance may still lead to imbalance in a small trial such as this. Variable blocking limited the possibility of guessing group randomization and assured equal distribution of the groups throughout the study duration.

STUDY POPULATION

The following inclusion and exclusion criteria were used when subject selection was conducted.

Inclusion Criteria

- American Society of Anesthesiologists (ASA) class 1-3
- Age > 18 years
- Duration of procedure 30-90 minutes
- Gynaecological ambulatory population

- Unpremedicated

The ASA classification describes a patients' physical status or health. Classes 1 to 3 were as chosen, which includes a range from healthy patients to those with severe, but not incapacitating systemic illness. We desired healthy patients who would be eligible for ambulatory procedures, yet did not want to exclude those with moderate / severe systemic illness who were deemed well enough for ambulatory procedures. The age of 18 years or greater was chosen as this was the age of ability to give consent. We chose Gynaecology patient population, as this group of patients was most readily available for study recruitment within my anesthesia practice. We chose not to have patients pre-medicated, as we did not want to confound our results by the use of preoperative benzodiazepines. Preoperative use of a benzodiazepine would also likely inhibit the use of intraoperative midazolam coinduction due to the perception of excessive postoperative sedation if two doses of benzodiazepines were given in combination.

Exclusion Criteria

- Pregnancy
- Previous sensitivity to any of the agents used including:
    - Propofol – constituents
    - Midazolam
- Psychoactive/narcotic medications during prior 1 week i.e.
    - Narcotics

    - Benzodiazepines
    - Barbiturates
    - Anti- epileptic medications
    - Anti- psychotic medications
- Not able / willing to provide informed consent
- Pre-existing cognitive deficits
    - Alzheimer's
    - Dementia
    - Developmental Delay

The use of propofol and midazolam is still not approved within the pregnant population. The remainder of the exclusion criteria was chosen again to prevent confounding of the study outcome assessments. Preoperative use of psychoactive medications may have influenced the assessment of cognitive function postoperatively, as might the existence of a pre-existing cognitive deficit. The DSST and the TDT scores were assessed using "norms" from varying age groups so it was therefore felt to be valid to exclude these groups.

ETHICAL CONSIDERATIONS

Application and full approval was obtained in April 1996 from the Human Investigation Committee (Appendix B) Memorial University of Newfoundland, Office of Research and Graduate Studies to be conducted at the Health Care Corporation (three

Hospital Sites). The study did not get conducted until a combined Clinical / Research Fellowship in Obstetric Anesthesia was secured in 1999 through an IWK Board of Directors Fellowship grant.

Application to the IWK-Grace Health Centre Research Ethics Committee was completed July 1999 and full approval was granted September 1999. This study followed MRC 1987 "Guidelines to Research Involving Human Subjects"[3].

Subjects were initially identified from published operating room lists and were deemed eligible based upon of type and duration of booked surgical procedure. Under the MRC 1987 guidelines it was acceptable for patients to be approached by non-primary caregivers to enrol in research trials. The principal investigator recruited patients the day of surgery, usually two hours before the scheduled operation.

Patients were given a copy of the consent form (Appendix C) and given time to consider if they would like to participate. The decision to enrol was purely voluntary with protection of patient rights. The patients understood that there was no compensation for study enrolment. Withdrawal from the study was possible and could be done at any time. Patients were to understand that this would not affect their subsequent anesthetic care. Consent was then obtained by one of the recruiters.

All patient records and data forms were kept strictly confidential. Subject names were not used on the data collection records and were only identified by randomization number. The investigator had a logbook in which the patient name / health record number recorded along with their randomization number. This was kept in a locked

[3] Now replaced with Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 1999

drawer in the Department of Anesthesia research office. Patients were offered access to the results of the study if they desired and the researcher was available at all times during the study to answer questions should they have arisen.

Recruitment of patients

Patients were recruited March to August 2000 from the gynaecologic ambulatory patient populations scheduled to under go elective laparoscopic procedures. Attending anaesthesiologists and the attending gynaecologists (Appendix E) had agreed to let the investigator approach suitable patients identified from published operating room lists. Contact with the patient was made through the Day Surgery / Same Day Admission waiting area, usually two hours before the scheduled procedure. If patients were interested and permission was granted, assessment of inclusion/exclusion criteria was done by the investigator. If these criteria were met, patients were invited to participate in the clinical trial with full explanation of the study protocol. Foreseeable risks and benefits including possible delay or improved time to discharge, possible cognitive impairment / improvement was explained.

OUTCOME MEASURES

Cognitive function is complex involving numerous aspects of cerebral function; i.e. sensory input processing, motor function, central processing, vigilance, memory, etc. There are a huge number of these tests that have been used to assess recovery from anesthesia. Individual neuropsychological tests generally assess one part of the complex

interaction of cognitive function. Ideally a complete set of tests would be compiled to assess all aspects of mental activity to give a global assessment of function. In practice, we limit tests we use as anesthesia affects all aspects of cognitive activity. Otherwise this set would be excessive. A minimum complete set of psychomotor tests post general anesthesia would assess perception, co-ordination and central activity (39). When using neuropsychological tests precautions must be taken to maintain construct validity. Individuals vary considerably in their baseline abilities, practice effects must be considered, and sophisticated tests may actually create interest therefore increase arousal and influence test results (39,66).

A minimum complete set of psychomotor tests post general anesthesia was constructed. It consisted of two objective measures of neuropsychological recovery the Digit Symbol Substitution Test® (DSST) and the Treiger Dot Test (TDT). It also contained 5 Visual Analogue Scales as a subjective measure. These tests were conducted preoperatively and postoperatively every thirty minutes once an Aldrete Score of 7 or greater was attained. Copies of these tests are included as Appendix D.

The DSST is a subset of the Wechsler Adult Intelligence Scale (56) battery of neuropsychological tests. These tests are used by psychologist to assess adult intellect / cognitive function. In the DDST sub-test the subject is presented numbers 0-9 to matching nonsense symbols. The task is to copy the appropriate numbers into boxes labelled randomly by the symbols. The score is the number of items substituted correctly in 90 seconds. If the test is repeated, a new set of numbers/symbols must be used to prevent learning. The Psychological Corporation, Harcourt Canada (the copyright owners

of the Wechsler Adult Intelligence Scale) was contacted and provided with permission four equivalent versions (by rearrangement of symbol / number relationships in a random fashion) of this test. Instructions were given according to the WAIS-r[4] administration and scoring manual. The DSST involves sensory input, central processing, motor co-ordination and ability to perform. It is a sensitive test to the effects of many anesthetic drugs including benzodiazepines on perceptual processing and coding / memory skills (39,43,48,57-59).

The Trieger Dot Test (TDT) was first described in 1969 and is a modified version of Design 4 of the Bender-Gestalt Test (60). Trieger et al modified the administration and scoring method to specifically assess recovery from anesthesia. The TDT requires the subject to draw a figure by joining 42 dots placed at 12-13 mm intervals. The number of dots missed, time taken to complete and error of magnitude (cumulative distance of miss in mm) from base line was originally described. Subsequent modifications have added a "timed" component and / or omitted the error of magnitude (35,49,61). This study measured the number of dots missed in 30 seconds. The TDT measures sensory processing / perceptual ability as subjects need to see the figure in the dots and motor co-ordination is needed not to miss the dots.

Subjective assessment of cognitive function was included in the battery of neuropsychological testing (Appendix D). Subjective measures of neuropsychological recovery consisted of five Visual Analogue Scales that were again scored every thirty minutes concurrently with the objective measures. The 5 different Visual Analogue

[4] This version has now been replaced with the WAIS-III

Scales (VAS) included as an assessment of patient perception and insight into their cognitive function (62). The five VAS 100mm scales asked patients to rate their feelings of drowsiness, confusion, co-ordination, anxiety, and sedation. As a measure of internal reliability of VAS scores, the assessment of level of consciousness was asked twice using two different descriptors i.e. feelings of drowsiness (alert / extremely tired) and feelings of sedation (wide-awake / almost asleep).

Validation of Neuropsychological Tests in Anesthesia

Bond and Lader (44) in 1972 found the DSST to be a sensitive measure of residual effects of benzodiazepines on human performance. These residual effects were observed to occur in a dose related manner. Chernik et al in 1982 (43) reviewed published studies to assess the effects of sedative-hypnotic drugs on human performance. This group made several conclusions after reviewing 52 studies assessing human performance on 15 "tasks" or neuropsychological tests. They concluded that different psychomotor performance tests are differentially sensitive to the effects of sedative-hypnotics and that there was consistent dose differences i.e. the higher the dose, the higher the performance decrement. They concluded long-acting drugs had more performance decrement but that the long elimination half-life could not be reliably used to predict performance effect over time. They also concluded that of the 15 tests assessed, the DSST was one of the four most sensitive tasks for assessing benzodiazepine effect on human performance. Subsequent studies have used the DSST as an objective assessment of psychomotor function after midazolam administration (57,59,61,63).

The TDT was validated in 1969 as a test of recovery from anesthesia. The test performance (improvement over time towards base line) was directly and significantly related to recovery as defined as period from awakening to discharge time (60). Subsequent reliability and validity has been shown (64) with studies were published for performance effects after narcotic, general anesthesia inhalation agents and benzodiazepines (including midazolam) (33,35,46,49,61).

The VAS scores were included to assess cognitive recovery for several reasons. Firstly, they are validated assessment tools of cognitive function in both benzodiazepine and general anesthesia assessment (48,57,61,67). Secondly they were used to correlate patient perception / insight of cognitive function with the objective measures.

Primary outcome

The primary outcome measure was the difference in DSST score as assessed at the 60 minute postoperative assessment adjusted for baseline preoperative score between the midazolam coinduction group and the standard propofol induction group.

The clinically significant change in DSST score to determine alteration in cognitive function was determined by looking at DSST scores in previously published work by Chernik and associates (57). This study used several assessment scales to assess alertness in subjects administered midazolam. Patients assessed at 60 minutes post midazolam administration "lightly sedated" had a mean score of 26.7, heavily sedated had a score of 13.7 and not sedated (placebo) 47.3. This yielded a clinically significant score of 13. The decision to not use the placebo baseline score of 47.3 was justified as it

was unlikely with residual effects of the general anesthetic agents / PACU analgesia would likely prevent attaining scores as low as placebo. Supporting this assumption was a study of general anesthesia using midazolam as an induction agent reported a DSST score of 36 at 60 minutes postoperative (61).

The sixty-minute time period was felt to the most clinically relevant assessment. This is the earliest time period in our institute when a patient would first be considered for discharge. It therefore is important to determine what the status of cognitive function recovery at that time would be. After this time period it is likely that the majority of patients would be discharged and attrition of subject numbers would likely prevent conclusions from data analysis. This is also the time period taken for our base-line estimate of DSST scores for heavy and light sedation.

Data Collection and Secondary Outcomes

Data were also collected on various intra-operative variables (table #2.1) and postoperative variables (table # 2.2) to assess other possible clinically significant outcomes that may differ between the two anesthetic techniques. This data was collected in the preoperative and postoperative periods. The intraoperative data and postoperative data were collected in the PACU from the perioperative record, the anesthetic record and the PACU record. The secondary outcomes included the Trieger Dot Test and the Visual Analogue Scale scores. The Trieger Dot Test and Visual Analogue Scale scores were included as part of the battery of objective measures of neuropsychological recovery. As previously discussed these were felt to be important in the overall assessment of the many

aspects of cognitive function. The other secondary outcomes included assessing effects of midazolam on intraoperative hemodynamics, total fentanyl (intraoperative narcotic dose), failure of induction rates (reliability), and adverse intraoperative events. During the post anesthesia period secondary outcomes included total morphine dose (postoperative narcotic use), length of PACU stay, Aldrete Scores and ondansetron rescue use (postoperative nausea / vomiting rates).

Table#2.1 Summary of variables for which data was collected during the intraoperative study period.

Intraoperative Variables
Procedure type
Start time
Finish time
Duration
Preoperative vitals
Intraoperative vitals every 15 minutes
Failure of induction
Propofol dose (mg/kg)
Fentanyl dose (mg/kg)
Midazolam dose (mg/kg)
Muscle Relaxant used
Anti-emetic prophylaxis
NSAIDS used
Adverse events

Table#2.2 Summary of variables for which data was collected during the postoperative study period.

Postoperative Variables
Aldrete Score
PACU narcotic requirements (morphine mg/kg)
PACU anti-emetic rescue
Discharge time
PACU length of stay

The secondary outcomes and data were collected to enable a more complete assessment of the impact of midazolam coinduction. The secondary outcome data may reveal unanticipated effects of midazolam coinduction upon other important anesthetic qualities. These include assessments of quality of induction, change in the incidence of postoperative nausea or analgesic requirements. The analysis of the TDT scores and VAS scores will hopefully support the findings on the DSST and allow a comprehensive assessment of cognitive function. Analyses of secondary outcomes may also allow hypothesis generation for questions that need to be further assessed.

SAMPLE SIZE CALCULATION

Formal sample size estimation was conduced a priori. This was based on the primary outcome variable Digit Symbol Substitution Test Score (56). The standard deviation and mean was obtained from previous work (57). The clinically significant change of 13 was arbitrarily determined by the difference in scores on DSST between light and heavy sedation after benzodiazepine sedation (57). Number that was calculated per group 35 and adjusted for dropouts is 43.

Sample Size Formula – Per group based on Independent Group Means[5]

$$\mathbf{n / group = 2\ [Z\alpha + Z\beta]\ \sigma / \Delta]^2}$$

where by $\mathbf{Z\alpha} = 1.96$

$\mathbf{Z\beta} = 0.84$

$\mathbf{\sigma} = 20$

$\Delta = 26.78\text{-}13.7$

$=13.0$

$$\mathbf{n / group = 2\ [Z\alpha + Z\beta]\ \sigma / \Delta]^2}$$

$$= 2\ [1.96 + 0.84] \times 20 / 13.0]^2$$

$$=2\ [2.8 \times 1.5]^2$$

$$= 35$$

$\alpha = 0.05$ two tailed test with equal allocation of Type 1 error in each tail (0.025)

$\beta = 0.20$

σ = DSST standard deviation

μ_1= light sedation mean DSST score
μ_2= heavy sedation mean DSST score
(Previously published work[5])

$\Delta = \mu_1 - \mu_2$ difference clinically significant difference between the group DSST means

Anticipated Dropouts / Non-compliance (R)

$\mathbf{R} = 10\%$ (estimated drop out rate)

$$\mathbf{n\ / group = n \times 1 / (1\text{-}R)^2}$$

$$= n \times 1 / (1 \times 0.10)^2$$

$$= n \times 1 / (0.9)^2$$

$$= 35 \times 1.23$$

$$= 43$$

Number that was calculated per group 35 and adjusted for dropouts is 43.

[5] Chernik D.A., Gillings D., et al Validity and Reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with Intravenous Midazolam Journal of Clinical Psychopharmacology 1990;10:4 244-251

THERAPEUTIC INTERVENTION

Subjects were randomised to either

Group A propofol 2mg /kg (control group) or

Group B midazolam 0.02mg/kg : propofol 1mg/kg (intervention group).

Clinical Protocol

All patients entering into the study received a standardised general anesthetic. The drugs, sequence of administration as well as the intubation and extubation of the trachea was to be essentially the same for all study subjects. This was to minimise any confounding effects that other concomitantly administered drugs / anesthetic techniques could have on the outcome assessments.

After placement of appropriate monitors, insertion of a peripheral intravenous catheter with good flow of physiologic saline or lactated Ringer's solution, induction of anesthesia was commenced. During preoxygenation both groups received fentanyl 2mcg/kg. If assigned to treatment **Group B** then midazolam 0.02mg/kg was also administered at this time. These drugs were flushed through the intravenous line with physiologic saline or lactated Ringer's solution for 2 minutes. After the two minutes had elapsed, the appropriate dosage of propofol was administered. Assessment of hypnosis was carried out after the completion of injection of propofol (approximately 3 minutes after administration of fentanyl and/or midazolam). Hypnosis was assessed by failure to respond to the verbal command "open your eyes", or loss of eyelash reflex. Failure of induction was treated with further propofol 0.5mg/kg and this was noted in the outcome

assessment.

Once the patient was observed to be apneic i.e. no spontaneous respiration for 15 seconds the anesthesiologist commenced mask and ventilation and intubated the trachea. Endotracheal intubation was facilitated by administration of succinylcholine (1.5 mg/kg) and / or rocuronium (0.6 mg/kg). Anesthesia was continued as appropriate for the surgical procedure. Anesthetic maintenance drugs consisted of 50% nitrous oxide with 50% oxygen mixture together with the volatile inhalation anesthetic sevoflurane (Sevorane AF™). Initial over pressure technique was permitted to attain an end tidal concentration of sevoflurane between 1-3%. Non-steriodal anti-inflammatory agents (ketorolac (Toradol®) or naprosyn (Anaprox®)) etc) were to be given unless contraindicated. Anti-emetic agents (ondansetron (Zofran®)) were permitted as clinically indicated. A standardised protocol specified intervention to anticipated common intraoperative events i.e. hemodynamic change, light anesthesia (need for additional inhalation anesthesia / narcotic) or additional muscle relaxant was provided. This was provided to maintain equivalence in anesthetic technique in all aspects except the administration of midazolam. The outline of the standardised anesthetic and interventions are detailed in Appendix F.

Required hemodynamic measurements included at least one baseline pre-anesthetic heart rate, blood pressure, and SpO2 measurements. Subsequent measurements were carried out 1-minute post intubation and at 15-minute intervals during the remainder of anesthetic maintenance[6]. Adverse events such as hemodynamic

[6] CAS Guidelines to the Practice of Anesthesia require vitals every 5 minutes on the anesthetic record.

compromise requiring treatment, bronchospasm, arrhythmia etc was recorded and included in data analysis.

Reversal of anesthesia was to be carried out in the usual manner using neostigmine 50 mcg/kg with glycopyrrolate 0.01mcg/kg as necessary. End tidal concentration of sevoflurane was to be less than 0.40% prior to extubation. Extubation was to be carried out as clinically appropriate and patients were to be transferred to the Post Anesthesia Care Unit (PACU) in the usual manner.

PACU assessments and administration of medications were completed as per unit protocol. This included hemodynamic and respiratory monitoring and assignment of Aldrete post anesthetic recovery score (36). Analgesia and anti-emetic medications to be administered as clinically indicated by assessment of pain sedation and nausea included:

Analgesia - morphine 2 mg –4mg IV PRN

Nausea - ondansetron (Zofran®) 4mg IV PRN

DATA RECORDS

Data and outcome assessments were collected on data collection records and scored by either the principal investigator or a fourth year medical student. Prior to data collection, assessors reviewed the Treiger Dot Test and the WAIS sub-test DSST administration, according to the published WAIS-r administration manual and previously published techniques. A research assistant, using the Statistical Package for Social Sciences (SPSS-) manually entered into a computer file from data collected on Data Collection Records (DCR) (Appendix G). Accuracy of manual data entry was checked

using the individual DCR and raw data print out sheets by the principal investigator. Outlying or missing data was also rechecked to ensure for accuracy of data entry.

DATA ANALYSIS

The statistical approach to this clinical trial is based upon the null hypothesis and logic of proof such that the study results either allow the investigation to accept or reject the null hypothesis.

H_o: $\mu_1 = \mu_2$

Ha: $\mu_1 \neq \mu_2$

The null hypothesis tested in this clinical trial "There is no clinically significant difference between 60 minute DSST scores in patients treated with midazolam coinduced general anesthesia compared to standard propofol induced general anesthesia".

The significant ρ value, or the probability of making a Type I error, was designated at 0.05. The probability of making a Type II error has been set at 0.20. This gives a slightly higher risk at accepting an incorrect null hypothesis.

Descriptive statistics were used to describe patient demographics. The baseline patient demographic variables will not be statistically compared as suggested by Altman (73). If appropriate randomization techniques have been utilised any differences in baseline characteristics between the treatment and control groups should occur by chance. This was a randomised study and consequently, by definition, any differences between the treatment and control groups are by chance.

Frequency counts; percentages, means and standard deviations were calculated for

various intraoperative and postoperative variables. Analysis of Covariance was used to analyse neuropsychological test results. Treatment effect with respect to the primary outcome variable DSST Score was first compared using Student's t-Test for parametric data and independent group means. Analysis of covariance for repeated measures was also applied, with baseline values serving as a covariate. This was to adjust for any observed inter-group difference at baseline in the outcome measures. A linear regression analysis of the data was also planned (time permitting) to determine if there are any variables or patient characteristics that predicted prolonged Post Anesthesia Care Unit stay.

The data from the secondary outcomes was analysed to support the findings of the primary outcome. Secondary outcomes, as previously mentioned, should be treated primarily as hypothesis generating not hypothesis testing. Analysis included both Student's t-Test and Analysis of Covariance where appropriate.

BUDGET

A copy of the trial budget is included as Appendix H

CHAPTER 3

Results

SUBJECT RECRUITMENT AND RETENTION

This study was pilot tested from February 8-17, 2000 on 4 subjects. The complete processes of screening, enrolment, consent; administration of the standardised anesthetic and outcome assessments was tested. Data collection records, including neuropsychological assessments, were assessed for ease of patient understanding and ease of data collection. There were no major problems identified and the pilot data were not included in the study results. Subject recruitment commenced March 27, 2000 and was completed August 21, 2000. During this time, study patients were recruited on average 2 days per week dependant upon the investigator availability and suitability of scheduled operating room cases / list.

Formal data collection was limited to patients enrolled in the study. Data were not collected on screened but non-enrolled patients. However, overall patient acceptance of recruitment into the study was perceived to be very high. Of patients screened but not enrolled (eligible based upon booked procedure and time) the most common reasons for exclusion were:

1) use of psychoactive medications / narcotics within one week of the study
2) use of preoperative sedative
3) language / communication difficulties.

During this time period 88 subjects were recruited and randomised to the study.

There were no subjects over the age of 65 and therefore according to predetermined stratification guidelines all randomization envelopes were removed sequentially from the age under 65 box. The break down of subject recruitment and retention including those subjects with incomplete data collection sets are depicted in figure #3.1.

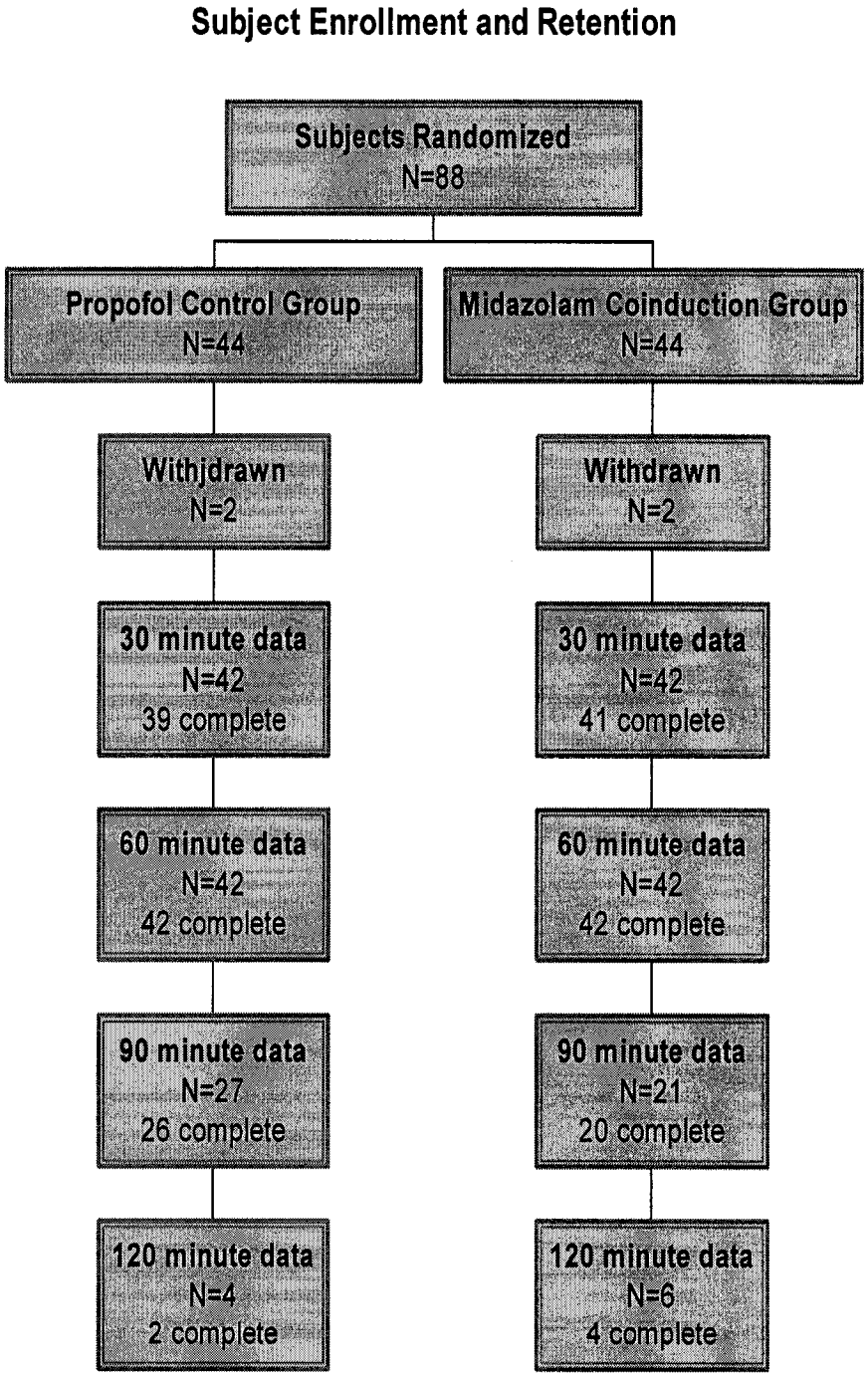


Figure #3.1 Subject retention while enrolled in the trial collection period. Number (N) of subjects not discharged and the number of completed outcome assessments for each collection period

Subject Dropout

Of the 88 patients entering the trial, four withdrew or were withdrawn from the trial before its completion. Two were assigned to the control group-propofol (**Group A**) and 2 were assigned to the intervention group–midazolam (**Group B**). Outcome assessments from these subjects were not included in the final analysis. The baseline data on these 4 subjects was collected for separate analysis. The details of subject dropout are provided.

Of the 4 subjects who did not complete the study, one patient was withdrawn due to intraoperative surgical complications (inadvertent bowel perforation with a subsequent 3-hour repair and colostomy). The duration of surgery and anticipated complicated postoperative course were cited as reasons for withdrawal. The remaining three subjects, who withdrew, did so in the Post Anesthesia Care Unit (PACU). Two of these patients refused to complete the outcome assessments due to post-operative nausea and / or vomiting. The third subject refused to complete the outcome assessments due to uncontrolled pain. These patients were approached 15 minutes after initial refusal to offer continuance in the study. All three subjects declined further study participation.

Subject retention

Eighty-four subjects completed the trial. Outcome assessments and data were collected every thirty minutes in the PACU until discharge. The earliest discharge (in accordance to IWK Health Centre institutional standards) was at 60 minutes. Of the 84 subjects who completed the trial, 10 subjects had 12 incomplete data collections (2

subjects had 2 incomplete data sets) prior to discharge from PACU. The last data set was completed at 120 minutes. These missing outcome assessments were evenly divided between the propofol control group and the midazolam intervention group.

At 30 minutes, 95.2% of subjects (eighty of a possible 84) had completed outcome assessments- 39 in the propofol control and 41 in the intervention midazolam group. At 60 minutes, 100% of subjects (eighty-four of a possible 84) had completed outcome assessments- 42 in the propofol control and 42 in the intervention midazolam group. At 90 minutes, there were 48 subjects still available for assessment in PACU. Of the 48 subjects, 95.8% or 46 outcome assessments were completed- 26 in the propofol control and 20 in the midazolam intervention group. There were 10 subjects still in PACU at 120 minutes. Of these 10, 60% or six had complete outcome assessments, 2 in the propofol group and 4 in the midazolam group.

Data up to and including the 60-minute data collection were included in the analysis. Eighty-four of the 84 subjects had complete data sets at the 60-minute data collection point. All data collection periods up to and including the 60-minute period had enough data collected for each subject to meet our sample size requirement of 35 per group. Because of the loss of subjects on discharge, analysis of data after this 60-minute data collection point lacks power and is more prone to bias due to potential differential loss across groups.

Baseline Demographics

Of the 84 patients who completed the trial, 42 received midazolam coinduced general anesthesia and 42 standard propofol induction. Of the 4 subjects who did not complete the study, 2 were randomized to the midazolam coinduction group and 2 to standard propofol control. Comparison of the baseline characteristics of those who completed the study by randomized group is provided in table 3.1.

Table 3.1 Comparison of Baseline Demographics by Randomized Group

	Propofol Control N=42 Mean +/-SD	**Midazolam Coinduction N=42** Mean +/-SD
Age (years)	32.9+/-6.4	31.7+/-6.2
Weight (kg)	68.9+/-12.9	71.5+/-17.4
	N (%)	N (%)
ASA class I **class II**	24(57.1) 18(42.9)	28(66.7) 14(33.3)
Procedure: **Diagnostic Laparoscopy** **Laparoscopic T/L**	20(47.6) 22(52.4)	21(50.0) 21(50.0)

Of the four subjects who did not complete the study, baseline demographics were collected and are shown in table #3.2. These demographics are compared to those subjects who did complete the study. There does not appear to be any difference with respect to age, weight, and ASA status or procedure type to distinguish this group from those who did complete the study.

Table 3.2 Baseline Comparison of Subjects whom Withdrew to those Completing the Study.

	Withdrawn from Study N=4	**Completed Study N=84**
	Mean +/-SD	**Mean +/-SD**
Age (years)	27(+/-2.9)	32.3(+/-6.3)
Weight (kg)	66.5(+/-8.6)	70.3(+/-15.3)
	N (%)	**N (%)**
ASA class I **class II**	3 (75%) 1(25%)	52(61.9) 32(38.1)
Procedure: **Diagnostic Laparoscopy** **Laparoscopic T/L**	 3(75%) 1(25%)	 41(48.8) 43(51.2)

As shown in table #3.1, the groups were comparable with respect to all baseline characteristics including age, weight, and American Society of Anesthesiologists (ASA) physical classification. The average age was 32.9 years for the control group versus 31.7 in the midazolam group. The average weight was 68.9kg compared to 71.5kg. Similarly the type of operative procedure was evenly distributed in both groups. Of the 84 operative procedures, there were 41 diagnostic laparoscopies, 20 in the propofol control and 21 in the midazolam group. There were 43 laparoscopic tubal ligations with 22 in the propofol group and 21 in the midazolam group.

OUTCOME MEASURES

Intraoperative Variables

Figure 3.2 shows the group averages, at different time points, for a range of hemodynamic measures including heart rate (beats per minute) and systolic and diastolic blood pressure (mmHg). Analysis by Student's t-Test for independent continuous data showed no statistically significant difference between the two groups.

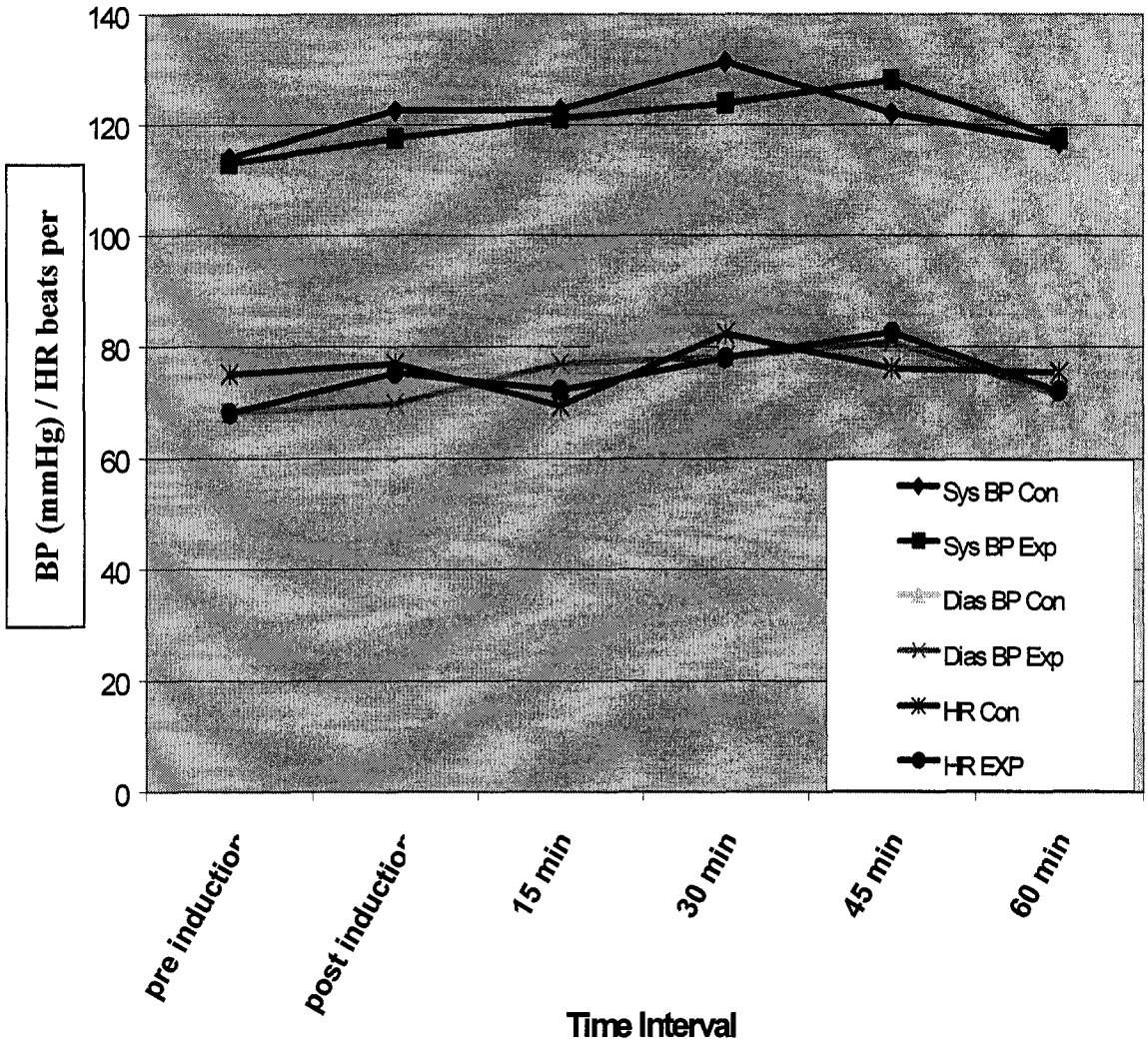


Figure 3.2 Intraoperative Hemodynamic Profile By Randomized Group. No significant difference noted at any measurement time points in heart rate, systolic or diastolic blood pressure

Groups were assessed with respect to various intraoperative variables (see table #3.3). Analysis was done using Student's t-Test for continuous data and Chi-Square / Fisher's Exact testing for categorical data. The purpose of these analyses was to determine whether there were any unexpected differences in the standardized general anesthetics administration or outcomes relating to the characteristics of the anesthetics that the two groups of patients received.

Table #3.3 Comparison of Intraoperative Variables based upon Group Randomization

	Propofol Control N=42 Mean+/-SD	**Midazolam Coinduction N=42 Mean+/-SD**	**95% Confidence Intervals (for the difference)**
Duration of Anesthesia (min)	41+/-16	43+/-16	-0.08, 0.005
Total Propofol Dose (mg/kg)	2.12+/-0.23*	1.19+/-0.32*	0.81, 1.04
Total Fentanyl Dose (mcg/kg)	2.24+/-.44	2.21+/-.47	-0.17, 0.22
	N(%)	**N(%)**	(for Relative Risk)
Subjects Failing Induction Requiring Supplemental Propofol	5 (11.9)	5 (11.9)	(RR 1.0) 0.31, 3.20
Received NSAIDS in OR	35 (83)	38 (90)	(RR 1.09) 0.92, 1.28
Received Ondansetron Prophylaxis	17 (40.5)	16 (38.1)	(RR 0.94) 0.55, 1.60
Occurrence of Adverse Events	3 (7.1)	2 (4.8)	(RR 0.67) 0.67, 3.79

* indicates $\rho < 0.000$

Table 3.3 demonstrates that both groups received comparable standardized anesthetics including anesthetic duration, dosages of fentanyl, prophylactic anti-emetic (ondansetron) and non-steroidal anti-inflammatory drugs (NSAIDS). This would support that there were no unrecognized confounding seen based upon these variables. The mean amount of propofol received was statistically significant as would be expected based upon study design and group randomization ($\rho<0.000$).

The number of patients (%) failing induction requiring supplemental propofol was exactly the same 5(11.9%) per group. This would indicate similar reliability of induction between the two techniques. The rate of failed induction (11.9%) is as expected or better as this study utilized the ED 50 dosages (ED 50 – estimated dosage to induce 50% of patients) for anesthetic induction agents used. The improved rate of failed induction likely can be accounted for by the addition of narcotic (fentanyl) during induction for both groups. Fentanyl was used primarily for its analgesia during surgery also has synergistic and additive effects on anesthetic induction. It is therefore often given at time of induction to improve quality and reliability of induction.

The incidence of adverse events was also recorded and analyzed for both groups. There were 3(7.1%) in the propofol control group compared to 2(4.8%) in the midazolam coinduction group, which did not meet statistical significance ($\rho= 1.0$). These adverse events are not uncommon and were felt to be minor in nature. They consisted of two intraoperative episodes of bronchospasm (increased airway pressures PaW > 35cmH_2O), two intraoperative episodes of bradycardia (heart rate <40bpm) and one episode of

hypertension / tachycardia with carbon dioxide insufflation of the peritoneum (responded to deepening anesthesia).

Post Anesthesia Care Unit Variables

Groups were also assessed with respect to various post anesthesia care unit (PACU) characteristics. These included standard assessments such as Aldrete Score and length of PACU stay. The requirements for postoperative analgesia and anti-emetic (PONV) rescue medications (see table #3.4) were also assessed. There were no statistically significant differences between groups in any of these variables based upon Students t-Test or Chi-square testing as appropriate.

All subjects were asked upon arrival in the PACU and just prior to discharge about recall of intraoperative events. No subjects reported any memories of the operative procedure itself or any intraoperative recall after "going to sleep".

Table # 3.4 Comparison of Post Anesthesia Care Unit variables based upon Group Randomization

	Propofol Control N=42 **Mean +/-SD**	**Midazolam Coinduction** N=42 **Mean +/-SD**	**95% Confidence Intervals** **(for the difference)**
Morphine Dose Received (mg/kg)	0.13+/-.10	0.13+/-.11	- 0.042 , 0.049
Length of PACU stay (min)	91+/-37	83+/-32	-0.07, 0.23
	N(%)	**N(%)**	(for Relative Risk)
Aldrete ≥7 on Arrival	35 (83.3)	36 (85.7)	(1.03) 0.86, 1.24
Received Ondansetron Rescue	13 (31.0)	12 (28.6)	(0.92) 0.48, 1.78

Table 3.4 demonstrates that the PACU stay for both groups were similar with respect to all variables including markers of physiologic recovery (Aldrete Score) and rate of postoperative nausea and vomiting (ondansetron rescue). The average length of stay in PACU was 1 hour and 31 minutes (+/-37) for the propofol control group and 1 hour and 23 minutes (+/-32) for the midazolam coinduction group. Similar numbers of subjects in both groups who received an Aldrete score of 7 or greater and /or received ondansetron rescue for PONV.

Assessment of Neuropsychological Recovery

The Digit Symbol Substitution Time and the Treiger Dot Test results conducted preoperatively and postoperatively every thirty minutes once an Aldrete Score of 7 or greater was attained. Greater than eighty percent of subjects in both groups had an Aldrete Score of 7 or greater an arrival in PACU. All patients had an Aldrete Score 7 or greater at time of first assessment (30 minutes). The five Visual Analogue Scales were also scored preoperatively and every thirty minutes concurrently with the objective measures.

The data were analyzed initially using Student's t-Test and secondarily with a general linear model analysis of covariance (ANCOVA) for repeated measures. Initial statistical analysis of cognitive function was completed using Student's t-Test for independent group means. The results shown in Figure # 3.5 are for the initial preoperative or baseline assessment. Student's t-Test was also used to compare the groups at the 30-minute (table 3.6) and 60-minute (table 3.7) intervals.

The repeated measures analysis using Analysis of Covariance (ANCOVA) adjusting for baseline preoperative scores utilized a full factorial model with simple within subject contrasts. The model included time as a within subject factor and group randomization as a between subject factor. The data were analyzed as previously noted up to 60 minutes using the preoperative value for outcome of interest as covariate in each case. Table 3.8 summarizes the statistical significance levels of cognitive recovery assessments. Tables 3.9 to 3.11 provide more detailed information with respect to the Analysis of Covariance (degrees of freedom, mean square, F value etc.) for each cognitive test.

As expected all these assessments except the VAS for anxiety showed a significant difference for all measures over time in both groups i.e. "wearing off" effect of the drug over time. This is expressed in the "Time" row in tables #3.8 through to #3.11

A test for interaction was also performed as shown in the "Time by Group Randomization" row in tables #3.8 to #3.11which specifically assessed whether there was a particular time point (i.e. 30-minute versus 60 minute measure) where the neuropsychological test results were more influenced by the randomized group assignment. There was no difference in the neuropsychological test results even at earlier time points based upon group randomization.

When analyzed for between subject factors for group randomization there was no difference in the neuropsychological assessments based upon whether the patient

received midazolam coinduction or propofol alone. This is expressed in the row "Group Randomization" in tables #3.8 through to #3.11.

Table # 3.5 Student's t Test comparing Neuropsychological Assessments between Midazolam and No Midazolam (control) groups at baseline (preoperative)

	Mean		Std Deviation		Significance Level ρ	95% Confidence Interval (of the difference)
	Midazolam N=42	Control N=42	Midazolam	Control		
DSST	64.6	58.9	12.1	12.4	0.03*	-11.12, -0.46
TDT	2.8	4.2	2.9	3.6	0.06	-0.03, 2.79
VAS 1	1.4	1.5	1.5	1.9	0.83	-0.66, 0.82
VAS 2	0.8	0.8	1.5	1.1	0.97	0.56, 0.55
VAS 3	0.5	0.7	0.3	0.7	0.07	-0.02, 0.44
VAS 4	3.6	3.1	2.5	2.2	0.36	-1.50, 0.54
VAS 5	1.2	1.2	1.3	1.2	0.93	-0.57, 0.52

* indicates $\rho < 0.05$

Table # 3.6 Student's t Test comparing Neuropsychological Assessments between Midazolam and No Midazolam (control) groups at 30 minutes Postoperative

	Mean		Std Deviation		Significance Level ρ	95% Confidence Interval (of the difference)
	Midazolam N=41	Control N=39	Midazolam	Control		
DSST	50.6	46.5	10.4	11.0	0.09	-8.92, 0.62
TDT	8.9	10.8	6.7	7.4	0.23	-1.25, 5.0
VAS 1	6.6	5.8	1.9	2.0	0.10	-1.6, 0.14
VAS 2	4.2	4.2	2.5	2.6	0.94	-1.10, 1.19
VAS 3	5.1	4.8	2.1	1.8	0.52	-1.18, 0.60
VAS 4	2.8	2.3	2.2	1.7	0.23	-1.42, 0.35
VAS 5	5.3	5.2	1.4	1.7	0.67	-0.81, 0.53

Table # 3.7 Student's t Test comparing Neuropsychological Assessments between Midazolam and No Midazolam (control) groups at 60 minutes Postoperative

	Mean		Std Deviation		Significance Level ρ	95% Confidence Interval (of the difference)
	Midazolam	Control	Midazolam	Control		
DSST	55.7	51.8	10.5	12.7	0.12	-9.01, 1.11
TDT	7.1	7.9	5.8	7.3	0.56	-2.02, 3.68
VAS 1	4.5	4.5	10.5	12.7	0.89	-1.11, 0.97
VAS 2	2.9	3.2	2.0	2.4	0.57	-0.68, 1.23
VAS 3	3.3	3.7	2.0	1.8	0.40	-0.48, 1.18
VAS 4	1.9	2.2	1.6	1.8	0.40	-0.42, 1.04
VAS 5	4.06	4.01	2.01	1.95	0.93	-0.90, 0.82

Table # 3.8 Summary of Significance (ρ) Levels for Outcome Variables up to 60 Minutes by Repeated Measures Analysis of Covariance Adjusted for Baseline

	DSST	TDT	VAS 1 Level of drowsiness	VAS 2 Level of confusion	VAS 3 Level of coordination	VAS 4 Level of anxiety	VAS 5 Level of Sedation
Time	0.01*	0.05*	0.00†	0.00†	0.00†	0.32	0.00†
Time x Group Randomization	0.50	0.30	0.33	0.65	0.15	0.11	0.98
Group Randomization	0.78	0.94	0.22	0.76	0.92	0.58	0.67

Tests of within subjects factors for time and between subjects factors for group randomization. Full factorial model, simple within subjects contrasts. * indicates $\rho < 0.05$ † indicates $\rho < 0.01$

Table # 3.9 Analysis of Covariance Repeated Measures Adjusted for Baseline Measures for the Digit Symbol Substitution Test and Trieger Dot Test Outcomes up to 60 minutes

	Digit Symbol Substitution Test				**Trieger Dot Test**			
	df	**MS**	**F**	**ρ**	**df**	**MS**	**F**	**ρ**
Time	1	119.6	6.35	0.01*	1	74.44	4.13	0.05*
Time X Group Randomization	1	8.55	0.45	0.50	1	19.00	1.09	0.30
Group Randomization	1	0.45	0.08	0.78	1	0.17	0.01	0.94

* indicates $\rho < 0.05$ † indicates $\rho < 0.01$

Table # 3.10 Analysis of Covariance Repeated Measures Adjusted for Baseline Measures for the Visual Analogue Scale Outcomes up to 60 Minutes

	VAS 1 Level of Drowsiness				VAS 2 Level of Confusion			
	df	**MS**	**F**	**ρ**	**df**	**MS**	**F**	**ρ**
Time	1	79.16	34.08	0.00†	1	49.80	28.80	0.00†
Time X Group Randomization	1	2.28	0.98	0.33	1	0.37	0.22	0.65
Group Randomization	1	5.26	1.54	0.22	1	0.45	0.09	0.76

* indicates $\rho < 0.05$ † indicates $\rho < 0.01$

Table # 3.11 Analysis of Covariance Repeated Measures Adjusted for Baseline Measures for the Visual Analogue Scale Outcomes up to 60 minutes

	VAS 3 Level of Co-ordination				VAS 4 Level of Anxiety				VAS 5 Level of Sedation			
	df	**MS**	**F**	**ρ**	**df**	**MS**	**F**	**ρ**	**df**	**MS**	**F**	**ρ**
Time	1	47.21	37.00	0.00†	1	1.54	1.02	0.32	1	53.50	41.35	0.00†
Time X Group Randomization	1	2.70	2.11	0.15	1	4.03	2.68	0.11	1	0.00	0.00	0.98
Group Randomization	1	0.003	0.01	0.92	1	0.81	0.31	0.58	1	0.45	0.18	0.67

* indicates $\rho < 0.05$ † indicates $\rho < 0.01$

Pharmacoeconomics

Comparison of intravenous anesthetic induction agent drug cost (based upon the average drug dosages used per group) for induction of general anesthesia was completed. The drug cost was obtained from the pharmacy director (personal communication 68) of IWK Health Centre formulary list prices for 2001. The control group received an average dose of propofol 2.12 mg/kg (145mg) for an estimated induction drug cost of $3.25. The midazolam coinduction group received an average dose of propofol 1.19 mg/kg (85mg) - cost of $1.62 and midazolam 0.02mg/kg (1.45mg) - cost of $0.52 for a total drug cost of $2.14. The induction drug cost savings based upon the coinduction technique was $1.11 per patient.

CHAPTER 4

Discussion and Conclusions

The purpose of this study was to assess the effect of midazolam – a short acting benzodiazepine on general anesthesia recovery. We wished to assess whether a low dose of midazolam as used in a coinduction technique altered the recovery characteristics of patients receiving this type of general anesthesia induction. This was compared to standard propofol induction of general anesthesia. We specifically wished to assess cognitive recovery as assessed by objective neuropsychological testing.

We also wished to look at other secondary outcomes to assess the similarity of the two anesthetic techniques with respect to anesthetic quality. These outcomes included quantitative and qualitative assessments of clinical parameters of general anesthesia such as adverse events rate, failure of induction and postoperative analgesia requirements. These were included to look for possible subtle clinical differences between the two techniques of induction that had not been previously recognized. Such differences between the two techniques might confound any study differences. The secondary outcomes were also included to support or refute previously hypothesized benefits of the coinduction technique. We however acknowledge that conclusions cannot be made upon these findings but may suggest a relationship that would require further study or evaluation to prove a causal relationship existed.

The study results will be discussed with respect to these objectives. Where possible the results will be compared to previously published work. In addition where possible clinical implications of the study results will be discussed.

REVIEW OF RESULTS

During the 5-month study period 88 subjects were enrolled and 84 patients completed the study. The data on the four subjects who did not complete the study was collected and analyzed. This group of patients did not appear to be demographically different from those subjects who did complete the trial.

Of the 84 subjects who did complete the trial, exactly half (42) were randomized to the midazolam coinduction intervention group and half (42) to the propofol control group. The *a priori* sample size estimate of 35 was therefore exceeded for both groups at all time periods throughout the study. Data was collected on the subjects after 60 minutes for potential further secondary analysis of predictors of "late stayers" or those who were not discharged after the expected 1 hour recovery time period.

As expected with appropriate randomization techniques the groups were demographically similar with respect to all base line characteristics including age, weight and American Society of Anesthesiologists classification. The type of laparoscopic procedure completed during the operation was also similar between groups.

While we feel it important to demonstrate the clinical similarity of the groups at baseline we did not look at the statistical differences. It is felt that the risk of unrecognized confounding that differences in age, weight, health status and procedural

differences is minimized by randomization. We did compare intraoperative and postoperative parameters to assess statistical differences. Differences would be particularly important if unexpectedly one of the groups experienced more postoperative pain with increased postoperative narcotic requirements. Any differences in cognitive function as assessed by testing may inadvertently be attributed to midazolam when possibly it may be associated with the higher narcotic administration in that group. Such a finding would be of clinical concern also, as it would have to be explored as to whether the two anesthetic techniques were indeed equivalent with respect to this clinical endpoint.

Age was felt to be an important possible source of confounding and so therefore was stratified for. There were no subjects enrolled in the age over 65 years and therefore no patients were randomized from this stratum. This likely is due to the disease processes / clinical indications within the group of patients that undergo diagnostic laparoscopy / tubal ligation. Clinically these patients are usually young, pre-menopausal and ovulating. Patients 65 and older do not fit this clinical description and are likely not to present for these types of laparoscopic surgery. As a result of this we cannot generalize our study results to patients over 65 years. This group should be assessed in subsequent studies before any conclusions for this age group can be made.

Intraoperative Variables

Intraoperative variables were assessed during anesthetic induction of general anesthesia and throughout the duration of the operative procedure. There were no

differences in hemodynamic parameters as measured immediately post induction / intubation and throughout the procedure. Previously published work indicates inconsistent hemodynamic response during coinduction.

McClune et al (22) and Elwood et al (28) found no statistically or clinically important difference in blood pressure or heart rate response. Miller et al (49) indicates that hemodynamic response to induction and tracheal intubation were similar in the placebo and two low dose ranges of midazolam used during a midazolam TIVA coinduction technique. The high dose midazolam coinduction group (0.045mg/kg) in this same study however showed a beneficial lack of blood pressure response to intubation. Delucia et al (27) indicate that there was a greater fall in blood pressure post induction and less increase in blood pressure response to intubation. It is unclear if this occurred in both the low and/or high dose midazolam groups used in this study. These findings are somewhat contradictory in clinical desired effect. It is desirable to minimize a large blood pressure response to intubation, but it is undesirable to have a greater fall in post induction blood pressure possibly indicating less hemodynamic stability. The current study found that the hemodynamic response was similar between the two study groups and I am therefore unable to support to the claims that midazolam coinduction may provide greater hemodynamic stability.

The dose used for general anesthesia induction is the ED 50 of the specific drug used. Therefore by definition up to 50% of subjects may fail the initial drug dose and require supplemental induction drug. This study used the ED 50 for propofol alone and the ED 50 of midazolam-propofol as determined by isobolographic and probit analysis.

The number of subjects failing initial induction dose (clinically defined prospectively) was exactly the same (11.9%). The low number of subjects failing induction is accounted for by the use of narcotic administration during the induction sequence. Fentanyl, when used as an induction agent acts additively with propofol (67) and synergistically with midazolam (16). The study is unable to support the hypothesis of Vinik and others (25,26) that midazolam coinduction provides less variability and more precise anesthetic induction sequence

The duration of the operative procedures, total intraoperative narcotic dose, proportion of subjects receiving non-steroidal anti-inflammatory drugs (NSAIDS) and postoperative nausea and vomiting prophylaxis (PONV) was comparable between the standard propofol and the midazolam coinduction group. This supports that the standardized anesthetic protocol was followed and that the exposure to intraoperative drugs including inhalation anesthetic volatile vapour was similar for a comparable time period. The total dose of propofol (mg/kg) was different between the two groups as expected based upon the randomized group assignment. The total drug dose of propofol was slightly higher than that assigned based upon group randomization due to rounding up to the nearest 10mg.

During general anesthesia patients are exposed to large numbers of drugs. The use of a coinduction technique requires the exposure of yet another drug. Theoretically this may expose patients to increased undesired drug interactions. Also during a coinduction technique midazolam is administered prior to the administration of propofol often while the patient is being preoxygenated. There is potential for sedation during the

pre-oxygenation period and potential risk of impairment of de-nitrogenation if there is unexpected respiratory depression. The rate of minor adverse intraoperative events was low: 3 patients (7.1%) in the control group compared to 2 patients (4.8%) in the intervention group. This is comparable to previously published event rates (69). These supports the suggestion of Vinik et al (25,26) regarding the safety of midazolam coinduction compared to routine propofol induction.

Postoperative Variables

Postoperative variables were collected once the subject was admitted to the Post Anesthesia Care Unit (PACU) again as secondary outcome measures. These consisted of standard PACU recovery assessments and assessment of postoperative pain (by narcotic requirements while admitted to the unit) as well as rate of postoperative nausea and vomiting (as determined by ondansetron anti-emetic rescue) between the two groups. There was no significant difference between the two study groups with respect to percentage of patients who had attained an Aldrete Score of 7 or greater on admission (85.7% midazolam compare to 83.3% control). There was also no significant difference in the length of stay in the PACU between the two groups. These measures of physiological recovery suggest similarity between the two anesthetic techniques with respect to crude measures of anesthetic recovery. These findings agree with earlier published work of Miller et al (49) and Elwood (28).

The total drug dose of morphine (mg/kg) received by the two groups was the same (0.13mg/kg). The percentage of patients who received ondansetron anti-emetic

rescue was also comparable (28.6% midazolam compared to 31% control). This suggests similarity in postoperative clinical parameters of postoperative pain and postoperative nausea and vomiting.

Neuropsychological Testing

The neuropsychological test battery consisted of the Digit Symbol Substitution Test (DSST), the Trieger Dot Test (TDT), and 5 Visual Analogue Scales (VAS). These were administered preoperatively, as a baseline measure and every 30 minutes in PACU until discharge once an Aldrete Score of 7 or greater was attained (indicating physiologic stability). These scores were initially analyzed using Students t-test for independent grouped means. T-tests were conducted on the baseline measures and on the 30 and 60 minutes measures. While we felt that baseline demographics did not need statistical comparison, we did wish to look at the baseline cognitive tests, as any difference would have implications on the interpretation and clinical relevancy of any group differences after the intervention. The initial statistical analysis revealed the only significant difference between the two groups on neuropsychological testing actually occurred in the baseline measure on the DSST (64.6 midazolam intervention compare to 58.9 control symbols substituted $\rho = 0.03$ with 95% CI for difference –11.12 to -0.46). This unfortunately indicated that there was a baseline difference in cognitive function as measured by the primary outcome assessment tool between the two groups prior to the study intervention. The other secondary measures in the test battery did not show any difference at the baseline.

A second issue of multiple comparisons was also recognized at this point in time. Multiple comparisons can lead to a much higher probability of making a Type I error (α = 0.05 + 0.05 + 0.05+ 0.05 etc). Statistically significant results and scientific conclusions must therefore be viewed cautiously when utilizing multiple comparisons over time on the same subjects. To minimize the possibility of making a type I error when conducting multiple analyses one may adjust the α downwards (commonly by dividing the α by the number of comparisons). Another approach is the Bonferroni method whereby the critical value for t to be declared significant is increased (the amount increased depending on the number of comparisons).

However it was felt to be more appropriate to utilize an Analysis of Covariance using a repeated measures general linear full factorial model with simple comparisons. Utilizing this statistical method also allowed adjustment for the baseline difference in the preoperative neuropsychological test results (as a covariate). It also allowed for within subject comparison of the effect of time on the neuropsychological test results. The between subject comparison was for group randomization to assess the effect of the intervention.

Analysis of Covariance as described revealed that all measures of cognitive function (except the VAS#4 for anxiety) had a statistically significant difference in effect over time (within subject comparison). This would be as expected as there would be a clinical "wearing off" of the general anesthetic drug effects over time as the patient recovered in the PACU.

Analysis of Covariance by group randomization (between subjects comparison) analyses revealed there was no difference in any of the tests of neuropsychological function. Specifically the Digit Symbol Substitution Test, our primary outcome variable did not reveal a difference at the 60 minute assessment and had a significance level of $\rho = 0.78$. The control average score was 51.8 symbols substituted while the midazolam intervention group had an average score of 55.7. The mean difference in DSST scores at 60 minutes was – 3.9. The a priori clinically significant difference was 13 symbols substituted. The 60-minute DSST t-Test 95% confidence interval for the difference was –9.01 to 1.11. The confidence interval crosses zero which allows us to be more confident that the data is consistent with a possible population mean difference of zero. I also note that the width of the confidence interval is narrow and the upper and lower bounds do not include a clinically relevant difference in the score for the DSST. This allows us to interpret this negative trial as having sufficient power to exclude such a difference. The lack of group differences on the secondary measures of neuropsychological testing (TDT and VAS scores) supports this assertion.

Of note, comparison was also made utilizing time and group randomization together specifically assessing whether there was a particular time point where the neuropsychological testing was more influenced based upon group randomization. There was no difference in the neuropsychological test results even at earlier time points based upon group randomization.

Subjective Assessment of Cognitive Recovery

The VAS #4 score (out of 10 cm) for anxiety did not show a significant effect over time. This could be explained by the apparent low overall level of anxiety as judged by the subject's preoperative ratings (3.6cm midazolam compared to 3.1 cm control (preoperative) which remained low both at 30 minutes-2.8cm compared to 2.3cm and 1.9cm compared to 2.2 at 60 minutes.

As a measure of internal validity of the VAS assessing the patient's perception of level of consciousness, two scales asking the same question were included (VAS #1 for drowsiness and VAS #5 for sedation). The scores were similar on both questions over the 3 time periods assessed.

The VAS assessments were included to measure the patient's ability to subjectively assess their cognitive recovery. This was measured by asking about feelings of confusion (VAS #2) and of coordination (VAS#3). These assessments revealed that neither measure had returned to baseline score at the time of discharge. Confusion: 0.8cm midazolam and 0.8cm control (baseline) compared to 2.9 midazolam and 3.2cm control (60 minutes). Coordination: 0.5cm midazolam and 0.7cm control compared to 3.3cm midazolam and 3.7cm control (60 minutes). This lack of return to baseline agreed with the objective DSST and TDT assessments. DSST: 64.6 score (midazolam): 58.9 score (control) at baseline compared to 55.7 (midazolam): 51.8 (control) at 60 minutes. TDT: 2.8 missed (midazolam) : 4.2 (control) at baseline compared to 7.1 missed (midazolam) : 7.9 (control) at 60 minutes. These findings suggest that patients may indeed be able to judge their own degree of cognitive impairment post general anesthesia.

Economics and Coinduction

Comparison of the anesthetic induction agent drug cost based upon the average drug dosages used per group was completed. The induction drug cost savings based upon the smaller total drug cost of a coinduction technique was $1.11 per patient. This calculation likely is not a realistic assessment of cost differences between the two techniques. This does not account for the added cost of an additional syringe, hypodermic needle or professional time needed to prepare the medication. There may also be associated drug wastage costs as propofol is supplied in 200mg single dose vial. The average propofol induction dose for single agent technique was 145mg, while the average propofol dose in the coinduction group was 85mg. Theoretically, the contents of the single dose vial of propofol should be discarded after each case. Midazolam may be used in more than one case as it is supplied as multi-dose vial. Practically, if prepared in a sterile manner most clinicians do not discard the contents of the opened vial (personal communication with department colleagues). If the remainder of the propofol vial were discarded as the manufacturer suggests then there would be no drug cost savings using the coinduction technique. There actually would be an extra drug cost associated with using midazolam.

The potential cost associated with earlier discharge from PACU was assessed. The difference of an 8-minute earlier discharge in the midazolam coinduction group was not statistically significant and is likely not clinically significant. It does however represent a 10% overall reduction (91 versus 83 minutes) in the time spent in the PACU. The calculation of potential cost savings in earlier discharge from PACU is complex.

There is local data on the cost per patient per hour admitted in the PACU ($65.00 per hour). Based upon cost per patient per hour admitted to PACU a difference of 8 minutes a saving of $8.67 would be estimated (personal communication # 70).

Patient discharge from PACU is influenced by factors other than the actual time that the patient is physiologically ready for discharge. Discharge from Canadian PACU's is no less than 1 hour after general anesthesia. Time to discharge may also be dependant upon the unit activity (if the PACU nurses are otherwise busy) and whether or not the responsible escort for the patient is available for discharge / transport. The other confounding factor on PACU cost containment arises from PACU staffing practice. Staffing is based upon the caseload per day with a minimum number of nurses per booked number of cases. The PACU has to be staffed by at least 2 nurses, require a minimum number of hours that can be worked per shift and are usually required to remain in the PACU unit until the booked shift is completed. This requirement maybe regardless of the presence of recovering patients in the unit. Earlier discharge within the Canadian health care system does not automatically mean that the nursing staff hours will be reduced. The likelihood of significant health care cost containment with respect to 8 minutes earlier discharge ($8.67) plus possible drug savings ($1.11) is felt to be negligible at best.

Intraoperative Awareness

There was no incidence of intraoperative awareness / recall in either study group during the study. This would be in keeping with previously published reports of

intraoperative awareness incidence (0.1- 0.2% by Lui et al (51)). In a study of this size one might expect one possible report of awareness. Due to the rarity of such an event the sample size estimated to show a protective effect of midazolam during coinduction would be prohibitively large. We are unable to comment on the protective effect of midazolam on intraoperative awareness as suggested by Miller et al (49).

CONCLUSIONS

In conclusion, this study shows that there is no clinically important difference in cognitive recovery, as assessed by the Digit Symbol Substitution Test, in ambulatory, age under 65 years, gynecologic patients undergoing elective laparoscopic procedures of short duration within patients receiving midazolam during a coinduction technique compared to standard propofol induction. These results appear to be supported by secondary measures of cognitive function using the Trieger Dot test and Visual Analogue Scales.

The assessment of other post anesthesia recovery features including Aldrete Score, length of PACU stay appear to be similar. Features such as postoperative nausea and vomiting and postoperative narcotic requirements are similar between the standard induction technique and coinduction. We therefore suggest that both standard recovery room assessments and cognitive assessments appear not to be different between the two induction techniques. There does not appear to be any adverse effects on recovery using a coinduction technique using very low dose benzodiazepines.

The study supports the idea of similarity between a standard induction and a coinduction technique with respect to all other intraoperative clinical parameters such as induction reliability, adverse events, and hemodynamic stability.The possible benefits with respect to induction reliability, safety and hemodynamic stability were not demonstrated. Firm conclusions with regard to these parameters cannot be reached from the current study and need to be formally assessed in future trials. The hypothesized economic benefits of drug costs or hospital costs (PACU / unplanned admission etc) were also not demonstrated in this trial. The last hypothesized benefit of possible intraoperative awareness could not be assessed due to the rarity of the event.

Finally, I would conclude that the coinduction anesthetic technique appears to be equivalent to standard single agent induction, specifically with respect to cognitive recovery, but also generally compared to other qualitative general anesthesia features. Practically, if individual anesthesiologists based upon the unproven belief that there are benefits of a coinduction technique such as an intraoperative recall protection then there do not appear to be any adverse post anesthesia recovery cognitive affects to deter its use.

CHAPTER 5

Problems and Limitations

This chapter contains a review of the limitations of this study including methodological issues identified after the study completion. This chapter will also review the unexpected difference in preoperative group scores for the Digit Symbol Substitution Test, the primary outcome measure. The choice of the clinically significant difference on this test will also be discussed with respect to the study conclusions. These discussions will address possible implications for future research in this area.

The implications of the prolonged time period taken to complete, analyze and disseminate the results of this study (including this thesis) will be discussed. The clinical relevance of the coinduction technique to current clinical practice as opposed to practice in 1995 will be discussed. The results of this study will be compared to other similar studies published in the interval between conception and dissemination of this study.

Blinding

This study is a double blinded trial such that neither the investigator completing the outcome assessments nor the patients were aware of group assignment. The anesthesiologist administering the drugs however was aware of the group assignment and drug administration. One might argue that this therefore is an open label, blinded endpoint study.

The unblindedness of the administering anesthesiologist could have been a potential source of bias. Despite the study requirement of administering a standardized anesthetic protocol, which included specific volatile inhalation agent endpoints, there is a possible range of concentrations that the patient could have received. At the time of this study we were unable to measure dose of inhalation agent used. It is possible that an unblinded anesthesiologist could have resulted in systematic differences in concentration of the inhalation agent possibly affecting recovery. The decision not to blind the attending anesthesiologist was based on patient safety, the fact they were not assessing outcomes and the cost savings of not requiring pharmacy to provided blinded syringes of study drug.

The Primary Outcome Measure

The Digit Symbol Substitution Test, part of the WAIS battery of tests was chosen as the primary outcome measure in a battery of neuropsychological tests to assess recovery of the multi-dimensional area of cognitive function. A baseline or preoperative assessment of cognitive function was conducted prior to the administration of either of the general anesthetic techniques. This was done to provide a measure of "usual" or "normal daily" cognitive function and therefore score on these tests. One would expect, with appropriate randomization techniques, that in the long run both groups should have comparable preoperative scores and testing for baseline differences should not be necessary. In fact, as argued by Altman, statistical comparison of baseline parameter distributions across randomized groups should not be done (73). Any differences seen

will be due to chance if the randomization has been carried out correctly. However, even with proper randomization, in studies of limited size, there remains a chance that baseline differences in important parameters may be seen. Such baseline differences have to be considered in terms of their clinical (as opposed to statistical) importance, as well as their strength of relationship to study outcome when judging their relevance as confounders.

As the DSST was the primary outcome for the trial, the baseline scores were assessed to assure similarity between the two treatment groups. The baseline administration of the DSST showed a difference of 5.7 symbols coded between the two groups prior to any study intervention. This was unexpected, as both groups demographically were similar in all respects including age, weight and ASA classification. The mean score on the DSST was 58.9 for the control group and 64.6 on the midazolam intervention group, for a mean difference of –5.7 (95% CI –11.12 to -0.46). This confidence interval does not include zero, thus suggesting that the two mean group scores on the preoperative DSST are different. There likely would be no way to prevent this unexpected finding in the future except to perhaps increase the study sample size.

Such a difference was not seen with the other tools within the neuropsychological test battery conducted preoperatively. This may be explained by the fact that different neuropsychological tests assess slightly different areas of cognitive function. This is the reason why a battery of tests is included. i.e. sensory input, central processing, vigilance, coding and motor coordination.

The a priori statistical approach to the DSST and TDT data analysis initially was to use Students' t test for independent grouped means. Given that the study involved repeated measures of the primary and other outcomes, a repeated measures ANOVA was arguably a more appropriate test for the primary outcome. Given the baseline difference in DSST scores, an Analysis of Covariance (ANCOVA) (repeated measures) with baseline value as covariate was employed to assess any impact of this potential confounder. These differences were not anticipated a priori and these adjustments to statistical approach were determined post hoc.

Clinically Significant Difference

This study concluded that based upon a predetermined clinically significant difference of 13 on the DSST score there was no difference detected on cognitive recovery between the two anesthetic induction techniques. The choice of a clinically significant difference of 13 was reassessed after the study completion. This choice of 13 was based upon the previous studies of Chernik and associates (57) that assessed the level of patient sedation 60 minutes after midazolam administration. The lightly sedated group had a score of 26.7 symbols substituted; heavily sedated 13.7 and placebo (not sedated) had 47.3 symbols substituted. On reassessment Chernik's group had a lower baseline score than either group in this study's baseline preoperative tests. Review of Chernik's original paper revealed that the 18 subjects enrolled in the study were of similar age (mean 34.5 years compared to 32.3 years in the subjects completing this study). The DSST administration appeared to be similar over a 90-second period and with different

versions used for subsequent administrations. The scoring may have been slightly different, as scores appeared to be the number attempted as opposed to the number correct in our current study. The number attempted however should have resulted in a higher average score compared to the number correct. The reason for the difference from our current study baseline is not readily apparent.

The clinically significant difference was determined to be 13 looking at the difference in heavily sedated compared to lightly sedated scores. We chose not to use the placebo / no sedation score as we felt that post general anesthesia subjects would likely not return to a placebo baseline. In retrospect however we really wanted to assess the return of baseline function (equivalent to placebo function) or possibly "street readiness". This study may therefore really show the difference of lightly sedated outcomes as opposed to return to baseline function.

A more accurate estimation of "street readiness" might have been to use the placebo score compared to the lightly sedated score. The difference between these two groups would have yielded a clinically significant difference of 20.6. Recalculation of sample size using the larger clinically significant difference of 20.6 would result in a sample size estimation of 30 subjects per group. To the extent that this argument is valid, it further supports the lack of clinically important differences in outcome between study groups in the current trial.

The whole area of neuropsychological testing and assessment of cognitive function is obviously an area of clinical and scientific expertise within the Psychology discipline. During the initial formative phase of this study members of Memorial and

Dalhousie Universities Departments of Psychology were contacted informally to help provide input about these cognitive assessments. If I were to conduct future research utilizing other areas of expertise, such as the previously mentioned, I would develop a formal association with the involved department / content expert and conduct the trial utilizing a multi-disciplinary approach.

Time Period of Study / Thesis Completion

This study as described in the background chapters was initially developed in 1994 / 1995 when midazolam was a newly marketed, short acting benzodiazepine. Clinical experience within the context of general anesthesia and specifically in a coinduction technique was limited. There was little published literature and this was a popular topic of discussion and area for proposed research.

The time from initial development of this study to final presentation was just over 7 years. First submission of the written thesis requirement for the degree in Master of Science was then completed December 2003. As a result of the protracted time taken to complete this project several unique issues were encountered. During this time period the patent expired on Hoffman LaRoche's proprietary production of midazolam (Versed®). Generic brands became available, marketing and thus clinical interest diminished and funding for such projects was further limited.

During this time period considerable clinical experience was gained using both midazolam and a coinduction technique. Literature searches were repeated at several different times throughout the duration of the project. There were no published works

found specifically looking at neuropsychological recovery and midazolam coinduction of general inhalation anesthesia. Further experience with the coinduction technique seemed to support the clinical impression that emergence from anesthesia possibly was delayed, but that recovery and discharge were not adversely affected. Thus despite diminished clinical interest; the study remained relevant as the question remained unanswered.

There were numerous clinical trials published looking at very similar questions using midazolam as a preoperative sedative and one TIVA coinduction study (50) assessing recovery using neuropsychological testing.

A remarkably similar study by Richardson et al (72) in 1997 assessed midazolam "pre-medication effect" on recovery after brief outpatient gynecologic laparoscopic surgery using the DSST and TDT as well as the standard markers of postoperative recovery. A unique feature of their study that makes it very comparable to the present study, and different from the numerous studies looking at midazolam pre-medication, was the timing and route of midazolam administration. Most pre-medication trials assessing midazolam recovery effects administer the drug either orally or intramuscularly at least 30 minutes or earlier preoperatively. Richardson et al administered the midazolam dose intravenously and at 10 minutes prior to the induction of general inhalation anesthesia. This sequence and timing could very easily be in keeping with a coinduction technique. Some authors (71) describe the administration of midazolam maybe up to ten minutes prior to administration of propofol as achieving the same coinduction effect as when given at one minute prior. The conduct of the general anesthetic and dose of midazolam was also very comparable to the present study.

Richardson et al showed midazolam-associated impairment on early assessment of DSST and TDT (15 and 30 minutes) but no difference on either test at 60 minutes. This paper I feel supports the present study in that there is no difference in neuropsychological recovery as assessed by neuropsychological tests when midazolam is used in very low doses as part of a coinduction technique (or immediately prior to induction as an "intraoperative pre-medication" in the Richardson case).

SUMMARY OF FINDINGS

The results of this study indicate no difference in cognitive recovery as assessed by neuropsychological tests after a midazolam coinduced technique versus propofol alone in short ambulatory gynecologic procedures. This study suggests, but does not prove, that there are no clinically important differences within standard parameters of general anesthesia such as hemodynamic stability, adverse events, induction reliability, or postoperative clinical parameters such as nausea and vomiting or analgesia requirements. No practical economically important differences were demonstrated in favour of using either technique. Lack of intraoperative recall and rarity of the event prevents any comment about potential protective effects of the coinduction technique. Further research in these areas of uncertainty needs to be completed before these remaining questions can be definitively answered.

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APPENDICES

APPENDIX A
Literature Search Strategy

LITERATURE SEARCH STRATEGY

National Library of Medicine Pubmed

1. Midazolam (MeSH)

AND

2. Anesthetics, General (MeSH) OR Anesthesia, General (MeSH) OR Anesthesia Recovery Period (MeSH) OR Post-operative Period (MeSH) OR Post-operative Care (MeSH) OR Post-operative Complications (MeSH) OR Post-op*(Textword) OR Anaesthes*(Textword) OR Anesthes*(Textword)

AND

3. Cognition (MeSH) OR Neurobehavioral Manifestations (MeSH) OR Neuropsychological Tests (MeSH) OR cognit*(Textword) OR Neurobehav* (Textword)

#1 AND #2 AND #3

Limited to English Language, Human Studies

ALSO searched Midazolam (MeSH) AND Anesthesia Recovery Period (MeSH)

APPENDIX B
Ethics Approval Letters

APPENDIX C
Consent Form

DISCIPLINE OF ANESTHESIA
FACULTY OF MEDICINE
DALHOUSIE UNIVERSITY
MEMORIAL UNIVERSITY OF NEWFOUNDLAND

CONSENT TO PARCIPATE IN BIO-MEDICAL RESEARCH

TITLE: Neuropsychological Recovery After Midazolam - Propofol Coinduced General Anesthesia

PRINCIPAL INVESTIGATOR(S): Dr. Dolores M. McKeen,
Dept. of Anesthesia
IWK Grace Health Centre
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INTRODUCTION:
You have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment. None of your legal rights are waived and the investigator, research doctor and hospital still have their legal and professional responsibilities.

Confidentiality of all information about you will be maintained by the investigator. You will be assigned a study number at the time of entry and will not be personally identified on any study documents or subsequent publications. The study documents will be locked and only the investigators will have access to them. Occasionally the Research Ethics Board may audit the records to ensure these standards are met. The investigator will be available during the study at all times should you have any problems or questions about the study.

1.PURPOSE OF THE STUDY

The purpose of this study is to find out whether it is better to use one drug at its normal dose or two drugs at much smaller doses at the start of a general anesthetic. General anesthesia means that the patient is completely asleep during the surgery. The drugs which will be used, propofol and midazolam, have been used on their own for years to make people sleep and they have been used in millions of patients. When these drugs are given together it is possible to give much smaller dosages than if they are used alone. We want to look at this to see if there are any differences between using one drug or both drugs after the operation is over. We need to see if patients are more sleepy or less sleepy and see how long it takes to think and talk clearly. We also need to see how well you remember and are able to follow simple instructions after your operation is over.

2. STUDY DESIGN

This study is a single centre study and is only being conducted at this hospital. You will be assigned to receive one drug or two drugs at smaller doses at random. The chance of being assigned to one or the other group is equal (i.e. flipping a coin). The drug dosage is decided by your anesthetic doctor based upon your weight. Only your anesthetic doctor will know what drugs you receive at the start of the anesthetic. The anesthetic doctor will know what drug group you are in by taking a numbered envelope from the study coordinator. After that you will receive the standard anesthetic drugs to keep you asleep until the surgery is over. How well you remember and think will be checked by observing you and asking you questions before you go to sleep and after you wake up in the recovery room. You will also be asked to complete some simple psychological tests using a pencil and paper. This will be done every thirty minutes until you are ready to go home.

3. DURATION AND FORESEEABLE INCONVENIENCES

This simple testing should take no more than 5 minutes to complete. If you are not feeling well enough to answer the questions then you may refuse. It is possible that you may have to stay a little longer in the recovery room if it is felt that you are not ready to be discharged. It is possible that research may involve risks that are currently unforeseen.

4. TREATMENTS FOR THOSE NOT ENTERING THE STUDY

If you decide not to enter this study, you will receive standard treatment.
Patients may obtain further information about this study and its results once completed by contacting the Research Services Office at 428-8765 or the principal investigator at the Department of Anesthesia at the IWK Grace at 420-6627.

I _____ the undersigned, agree to my participation in the research study described.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee that I will benefit from my involvement. I acknowledge that a copy of this form has been given to me.

_____

(Print Name) (Signature of Participant) (Date)

_____

(Print Name) (Witness Signature) (Date)

To be signed by investigator

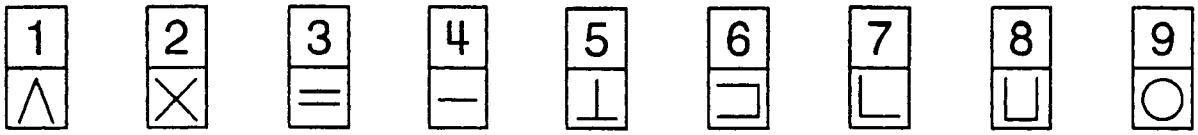
To the best of my ability I have fully explained to the subject the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understands the implications and voluntary nature of the study.

_____

(Print Name) (Signature of Investigator) (Date)

Appendix D
Neuropsychological Tests

Digit Symbol—Coding (Form D)



Sample Items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

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

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

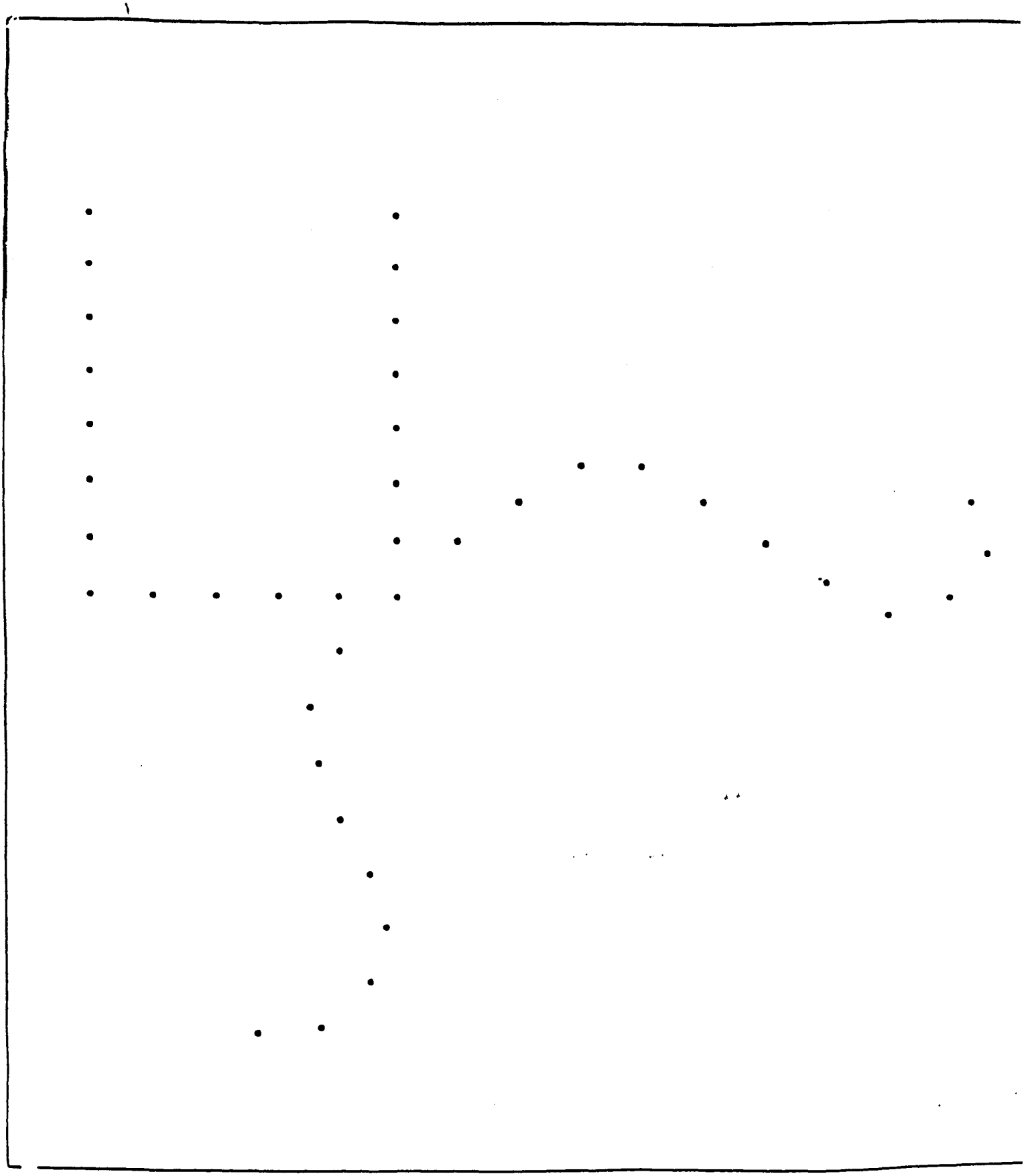
6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

TRIEGER DOT



STUDY CODE NUMBER_____ TIME ADMINISTERED_____

The questions below ask you to make a mark on a line relative to how you feel about the statements. The is no right or wrong answer- you simply mark the line based on your feeling or opinion.

Example:
The room is hot.

If you felt cooler you might mark here	*or here if you felt more warm*
_____X_____	_____X____
Completely Disagree	Completely Agree

1.Overall comment on how drowsy you feel.

Alert	Extremely tired

2. Comment if you feel any confusion.

Clear Headed	Fuzzy Headed

3.Comment on your overall feelings of coordination.

Well Coordinated	Extremely Clumsy

4. Comment on your level of anxiety.

Calm/ Relaxed	Extremely Nervous

5. Comment on your overall feeling of sedation.

Wide awake	Almost asleep

Appendix E
Letters of Permission

FEE-WAIVED PERMISSION AGREEMENT

This AGREEMENT entered into as of **OCTOBER 15, 1999**, between The Psychological Corporation, a Harcourt Assessment Company, 555 Academic Court, San Antonio, Texas 78204-2498 (herein the "Publisher") and

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ADDRESS: 5850/5980 University Avenue
P.O. Box 3070
Halifax, Nova Scotia B3J 3G9
CANADA

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Appendix F
Standardized Anesthetic Induction Protocol
and
Rescue Protocol

INDUCTION ALGORITHM

1.OPEN ENVELOPE –Inside will be the study group assignment
i.e. **GROUP(A) propofol 2mg/kg**
GROUP(B)midazolam 0.02mg/kg and **propofol 1 mg/kg**

2.DRUG DOSAGES-Draw up drug dosages as appropriate for the patient's weight and study group assignment (already calculated on the envelope).

3.MONITORS-Apply usual monitors prior to induction
i.e. SPO2 / ECG / NIBP etc

4.START INTRAVENOUS-Appropriate size angiocatheter with either free flowing normal saline or lactated ringer's solution.

5.DRUG ADMINISTRATION-**Group A and B -fentanyl 2mcg/kg** over 15 seconds

-If **Group B –midazolam 0.02mg/kg** over15seconds
-Note exact time of administration (2400h)

MUST WAIT 2 MINUTES
BEFORE INDUCTION SEQUENCE COMPLETED

-Propofol- If study **Group A-2mg/kg**
- If study **Group B-1mg/kg**

6.ASSESS HYPNOSIS-Assess induction in your usual manner
i.e. ask the patient to 'OPEN YOUR EYES' or
check eye lash reflex etc.

IF APNEIC > 15 SECONDS ASSIST VENTILATION
IF INDUCTION FAILS AFTER 60 SECONDS MAY ADD

SUPPLEMENTAL PROPOFOL 0.5mg/kg

IF STILL AWAKE PROPOFOL AS NECESSARY (PROTOCOL FAILURE)
Note reason why any additional propofol given on group assignment sheet

7.IF INDUCED - Muscle relaxant of choice
i.e. **Succinylcholine(1.5mg/kg)** or **Rocuronium(0.6mg/kg)**
-Intubate as usual.

8.MAINTENANCE OF ANESTHESIA – as clinically appropriate
i.e.-**N2O/O2** –50/50% End tidal
-**Sevoflurane** – 1-3% End tidal
-Supplemental **Fentanyl/muscle relaxant** as necessary
-**Naprosyn 500 mg PR** or **Toradol 30 mg IV** unless C/I
-**Ondansetron 4 mg** if an anti-emetic desired

9.LABEL ANESTHETIC RECORD- The study number will be on the envelope. Write this on the anesthetic record where propofol/midazolam dosages would be recorded. All other drugs maybe noted on the anesthetic record. Write the study number and the total amount of propofol/ midazolam given on the each half of the paper; tear and seal in envelope. Leave with chart it will be attached to the consent for immediate unblinding and one with study data collection record.

10.REVERSAL OF ANESTHESIA - Reversal as necessary
i.e.- **Neostigmine 50 mcg/kg / Glycopyrolate 0.01mg/kg**
-End tidal **Sevoflurane <0.40%**
-Extubate as clinically appropriate
ie. eye opening / spontaneous respiration / reaching for ETT

11.TRANSFER TO PACU Analgesia and anti-emetic as necessary
i.e. Prefer Morphine / Ondansetron prn

RESCUE PROTOCOL

Response to surgical stress:

Blood Pressure: increase in systolic BP > 30mm Hg above baseline lasting > 1 minute

Heart rate: increase in HR >110 bpm lasting > 1 minute

Somatic: limb movement / swallowing / grimacing

Autonomic: tearing / dilated pupils / diaphoresis

If these responses are not attributable to hypovolemia they may be treated with increasing the end tidal concentration of **Seveflurane 1 – 3 %** . If then required supplemental **fentanyl IV** may be given as clinically indicated. If the attending Anesthesiologist then feels that there is an adequate level of anesthesia and the patient is still hyperdynamic they may add a β **blocker** of their choice such as Esmolol or Labetolol.

Hemodynamic compromise:

Blood Pressure: decrease in systolic BP < 90mm Hg or a decrease from baseline systolic blood pressure of greater than 30% for > 1 minute. The end tidal concentration of **Sevoflurane** may be decreased and/or vasopressor agent may be given ie. **ephedrine/phenylephrine**

Heart rate: decreased heart rate < 40 bpm cholinergic antagonist may be given i.e. **atropine** 0.01mcg/kg

APPENDIX G
Data Collection Record

NEUROPSYCHOLOGICAL RECOVERY AFTER MIDAZOLAM - PROPOFOL CO INDUCED GENERAL ANAESTHESIA

PATIENT DOCUMENTATION AND TESTING MATERIALS

RANDOMIZATION NUMBER : _____

INVESTIGATOR : _____

ANAESTHESIOLOGIST _____

RANDOMIZATION # _____

DATE _____

AGE _____

WEIGHT _____

ASA _____

SURGICAL PROCEDURE _____

TIME INDUCTION STARTED (2400H) _____

TIME OF EXTUBATION/EMERGENGE(2400H) _____

TOTAL LENGTH OF ANAESTHETIC (MINUTES) _____

PERIOPERATIVE DATA

HEMODYNAMIC PROFILE	PRE-OP	POST-INTUBATION	15 MINUTES	30 MINUTES	45 MINUTES	60 MINUTES	90 MINUTES
HEART RATE							
SYSTOLIC BP							
DIASTOLIC BP							

FAILURE OF INDUCTION? _____

PROPOFOL (TOTAL MG DOSE) - _____ (MCG/KG) - _____

FENTANYL (TOTAL MCG DOSE) - _____ (MCG/KG) - _____

MIDAZOLAM (TOTAL MG DOSE) - _____ (MCG/KG) - _____

OTHER DRUGS (DOSAGES) GIVEN - _____

ADVERSE INTRA-OPERATIVE EVENTS? YES OR NO

EXPLANATION: _____

_____

_____

POST OPERATIVE / PACU DATA

TIME TO REACH ALDRETE SCORE 7 OR >(MINUTES) _____

NARCOTICS ADMINISTERED IN PACU? - YES OR NO
- TOTAL DRUG DOSE GIVEN _____

ANTI-EMETICS ADMINISTERED IN PACU? - YES OR NO
- DRUG/ DOSE GIVEN _____

UNABLE TO COMPLETE TESTING AT ANY POINT? – YES OR NO
ie. PATIENT WITHDRAWL; NAUSEA
EXPLANATION:_____
_____
_____

NEUROPSYCHOLOGICAL TESTING

	PRE OPERATIVE BASELINE	30 MINUTE/ 1ST MEASURE	60 MINUTE MEASURE	90 MINUTE MEASURE	120 MINUTE MEASURE	150 MINUTE MEASURE
TREIGER DOT TEST (#MISSED/42)						
DIGIT SYMBOL SUBSTITUTION (#CORRECT/ #COMPLETED)						
VISUAL ANALOG SCORE #1						
#2						
#3						
#4						
#5						

TIME TO DISCHARGE -_____

APPENDIX H
Budget

BUDGET

The following provides an estimate of the spending budget for this clinical trial.

Direct Costs

1.	Clinical /Research Fellow Salary -$47,809 per annum provided by IWK Grace Board of Directors Fellowship -40% research time (.40 x 47,809=19,123.60)	No net cost
2.	Materials/Supplies	
	-Computer/Statistical Software	3500.00
	-Photocopying	500.00
	-Secretarial	200.00
	-Telephone	250.00
	-Literature Search	50.00
	-Testing Materials - WAIS kit	300.00
		4800.00
3.	Clinical Presentation/Travel	2000.00
4.	Medical Surgical Supplies -propofol 20ml $5.52 -midazolam 2ml $1.07	Standard therapy should impose no cost
		No net cost

Indirect Costs

-30% of 20,323.60 = 6097.08 -As study is research driven, not industry driven This 30% cost is not applicable	No net cost
TOTAL	6800.00