Intravenous (IV) induction agents are used in anesthesia practice to facilitate the patient's smooth transition to unconsciousness and intubation. The specific actions desired of an induction agent are hypnosis and inhibition of protective airway reflexes. The ideal induction agent should provide these actions without the side effects of respiratory or cardiac depression, nausea, vomiting, or anaphylaxis. In addition, it should have a short duration of action and be inexpensive.¹ No individual induction agent has been shown to possess all of these characteristics, but the 2 agents that meet most of the criteria are thiopental and propofol.

The barbiturate thiopental has been the primary IV induction agent for more than 50 years and is considered the standard by which newer induction agents are judged.² Thiopental's mechanism of action is thought to involve occupation of -aminobutyric acid receptor sites on central nervous system chloride ion channels. This results in potentiation of cell membrane chloride ion conductance and neuronal inhibition. Thiopental is highly lipid-soluble, produces unconsciousness in fewer than 30 seconds, and has a short distribution half-life, with a termination of action within 4 to 15 minutes.³,⁴ Conversely, thiopental has an elimination half-life of 18 hours, and because of this, some practitioners believe it can result in a long-lasting sedative effect and a delay of emergence from anesthesia.¹

Thiopental also is associated with some adverse effects and reactions. For example, thiopental can cause a decrease in blood pressure, respiratory rate, and cardiac output, with a compensatory increase in heart rate via an uninhibited baroreceptor reflex.³ Thiopental also has been linked to causing an exacerbation of porphyria, bronchospasm, myoclonus, hiccoughs, and laryngospasm in people with asthma, and it can cause significant venous irritation when injected.³,⁴ In addition, thiopental has been shown to produce a hyperalgesia when given in subhypnotic doses, which can result in a decrease in analgesic efficacy for most opioids and analgesics.³ Despite these problems, thiopental remains the "gold standard" for induction agents because it is reliable and inexpen-

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Comparison of the Effects of Propofol Versus Thiopental Induction on Postoperative Outcomes Following Surgical Procedures Longer Than 2 Hours

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The use of propofol as an induction agent for surgeries lasting less than 2 hours has been shown to result in a faster emergence from anesthesia. Our study was performed to analyze the impact of propofol on surgical procedures lasting longer than 2 hours.

A convenience sample of 84 men and women undergoing nonemergency laparoscopic procedures scheduled for longer than 2 hours were enrolled in this prospective study and randomly assigned to receive a standardized induction with thiopental or propofol. Nausea and pain were measured using a 0 to 10 verbal numeric rating scale. Recovery from anesthesia was measured using a modified Newman Bender Motor Gestalt Test. Statistical analysis was used to analyze all ordinal and interval data. A P value of less than .05 was considered significant. No differences were found between the propofol and thiopental groups in demographics, total surgical time, anesthesia time, recovery times, postoperative analgesic and emetic requirements, satisfaction scores, or incidence of nausea and vomiting. Discharge times from the postanesthesia care unit and to home were similar between groups.

Based on the results, we concluded that propofol offered no advantages over thiopental in postoperative outcomes in laparoscopic surgical procedures longer than 2 hours.

Key words: Propofol, recovery profiles, thiopental, wakefulness.
Propofol is a newer IV induction agent that has been available for approximately 10 years. It is unique in that it is structurally unrelated to other agents and has been available for approximately 10 years. It is unique in that it is structurally unrelated to other agents and is prepared in a lipid suspension. Like thiopental, propofol’s primary site of action is believed to be the -aminobutyric acid receptor sites of chloride ion channels, where it causes neuronal inhibition. Propofol is highly lipid-soluble, and like thiopental, has an average onset time of approximately 30 seconds. Unlike thiopental, propofol is suspended in a lipid medium, which allows for a high volume of distribution (60 L/kg); thus, propofol is displaced readily from tissues, leading to a termination of action in 3 to 10 minutes and an elimination half-life of 4 to 7 hours. Because of this much shorter elimination half-life, many practitioners use propofol because they believe that patients experience a smoother transition to emergence and a faster recovery of wakefulness.

Propofol is associated with adverse reactions. Propofol reduces blood pressure and cardiac output by lowering systemic vascular resistance. In addition to this direct reduction in the systemic vascular resistance, propofol causes a blunting of the baroreceptor reflex, thus preventing compensatory tachycardia. Propofol also can irritate veins and can cause a dose-dependent reduction in respiratory rate, respiratory volumes, and ventilatory responses to hypercarbia. In addition, propofol should be used with caution in people with disorders of lipid metabolism because these disorders can alter its absorption and metabolism of propofol. However, propofol is less likely than thiopental to produce bronchospasm and laryngospasm and is better tolerated by people with asthma. At least 1 study indicates that propofol may cause some hypoalgesia, thus decreasing analgesic requirements. Propofol also has been implicated in causing a decrease in postoperative antiemetic requirements because some studies have reported that propofol can be effective in providing prophylaxis against postoperative nausea and vomiting following general anesthesia. Finally, propofol is more expensive than thiopental, costing approximately $7.73 for an induction dose of 2 mg/kg for a 70-kg person.

Heretofore, comparisons of postoperative recovery following administration of propofol or thiopental have been based on surgical procedures shorter than 2 hours. However, many surgical procedures last longer than 2 hours. It is unclear whether induction of general anesthesia with propofol has significant long-term benefits over thiopental in such cases. The purpose of this study was to compare the effects of propofol and thiopental on postoperative outcomes in adults who underwent surgical procedures longer than 2 hours. The outcomes we focused on were nausea, vomiting, pain, and psychomotor function as the subjects progressively recovered from a standardized general anesthetic and induction with thiopental or propofol.

Methods
A convenience sample of 84 men and women scheduled for nonemergency laparoscopic procedures that were expected to last 2 or more hours were enrolled and consented in this randomized, prospective, institutional review board–approved study. Subjects were excluded if they had a known sensitivity to any of the medications used in the study or had a history of hepatic, renal, or respiratory failure. In addition, subjects who reported a history of chronic pain, significant nausea and vomiting, or the presence of sepsis, or who were pregnant also were excluded from the study.

Subjects scheduled for intra-abdominal laparoscopic procedures of 2 to 3 hours’ duration were approached for inclusion in the preoperative anesthesia clinic, and parameters of the study were outlined. However, duration of the surgical procedure was analyzed as an independent variable; thus, if the surgical procedure exceeded 3 hours, subjects were not excluded from analysis.

After informed consent, subjects were assigned randomly to the thiopental or propofol groups by using a random numbers table. Demographics that included age, sex, height, weight, and ASA classification status were obtained preoperatively and recorded on the data collection sheet for all subjects. Nausea and pain were measured as separate variables using a 0 to 10 verbal-numeric rating scale (VNRS). The VNRS has been proved a reliable measure of pain and nausea intensity, translating a subjective symptom into a numerical value. This VNRS was performed preoperatively to serve as a baseline and every 15 minutes from admission to discharge from the postanesthesia care unit (PACU). Subjects were asked to rate nausea and pain separately on 2 continuous scales with one anchor point at 0, which indicated “no nausea” or “no pain,” while the other anchor was placed at 10, indicating the worst nausea ever experienced or the worst pain ever experienced.

Mental functioning, fine motor skills, and recovery from anesthesia were measured using a modified Newman Bender Motor Gestalt Test (NBMGT). This test is used routinely to measure a patient’s recovery from anesthesia because it allows for a direct
measurement of visual and motor activity through the performance of a series of hand and eye coordination drawings. The NBMGT is based on the original test designed by Bender in 1946 called the Bender Motor Gestalt Test, which is based on the assumption that fatigue produced by central nervous system depressants tends to exaggerate disturbances in the visual and motor coordination processing centers. In 1969 Newman et al adapted the Bender Motor Gestalt Test to its present model (NBMGT), which involves having the subject make a drawing by connecting dots on a piece of paper to form an outline of an open square with a tangential curved line (Figure 1). This adaptation of Bender's original test was easier to use in clinical scenarios and sensitive for the measurement of recovery profiles. Since its introduction, the NBMGT has become one of the primary tools used in many investigations to measure the return of a patient's visual and motor coordination and recovery from general anesthesia.

In the present study, subjects performed the NBMGT preoperatively, to obtain a baseline, and postoperatively immediately on arrival in the PACU and at 15-minute intervals thereafter until discharge from the PACU. The variables that were directly measured from the NBMGT included the number of dots missed, the summed distance (in millimeters) that the subject's line fell from each dot missed, and the number of extraneous deviations noted on the drawing. The drawings then were measured and compared with preoperative (baseline) measurements to determine the rate of return of motor function and visual acuity for each subject following exposure to the anesthetic and induction agents.

Preoperatively, all subjects were medicated with up to 2 mg of IV midazolam, based on individual needs or practitioner preferences. On arrival in the operative suite, monitoring equipment was applied, which included noninvasive blood pressure, electrocardiogram, and arterial hemoglobin oxygen saturation measurements. These measurements were recorded at 1- to 5-minute intervals throughout the operation. Anesthesia was induced by using thiopental or propofol based on the subject's group assignment. The subjects in the thiopental group were given 4 mg/kg of thiopental intravenously, while those in the propofol group were given 2 mg/kg of propofol intravenously.

Intubation of the trachea was achieved using a nondepolarizing or a depolarizing muscle relaxant based on individual practitioner preferences or surgical requirements. All subjects were intubated with an appropriately sized endotracheal tube, and an orogastric tube was inserted after intubation. Anesthesia was maintained with anesthesia inhalation agents of 50% oxygen/50% nitrous oxide and 0.5% to 1.5% isoflurane, titrated to effect. Fentanyl was the only opioid used intraoperatively and was titrated to effect, up to a maximum of 10 μg/kg IV. Reversal of muscle relaxation was accomplished using 0.05 mg/kg of neostigmine and 0.01 mg/kg of glycopyrrolate. Approximately 10 minutes before extubation of the trachea, the orogastric tube was discontinued and all subjects were given 4 mg of ondansetron and 30 mg of ketorolac intravenously. Immediately before discharge to the PACU, the total anesthesia and surgical time, the range of isoflurane, and the amount of fentanyl used intraoperatively were documented.

All subjects were extubated before transport to the PACU and had orders written for pain, postoperative tremor control, and nausea control. These orders included the following medications: (1) morphine sulfate, 1 to 3 mg intravenously every 5 minutes for pain as needed, not to exceed 0.15 mg/kg; (2) meperidine, 12.5 mg intravenously 1 time, given when needed for postoperative shivering; and (3) ondansetron, 4 mg intravenously, for complaints of nausea as needed, not to exceed 8 mg. Total analgesic and antiemetic requirements were recorded for all subjects on the data collection sheet before discharge from the PACU.
Before initiation of the study, all nursing personnel in the PACU were educated about use of the NBMGT and the variables required to be recorded on the data collection sheet. These variables included incidence of nausea, vomiting, or both; time and dose requirements for analgesics; and the frequency and dose of ondansetron used. In addition, all subjects were assessed by PACU nursing personnel on admission and discharge from the PACU using a 0 to 10 Aldrete score, which also was noted on the data collection sheet. All study measures taken in PACU were recorded up to 120 minutes after PACU admission.

Once discharged from the PACU, all subjects were transferred to the ambulatory procedures department (APD) or admitted to the hospital. For subjects transferred to the APD, their APD records were reviewed to determine whether any additional antiemetic and analgesic medications were needed after discharge from the PACU. For subjects admitted to the hospital, a review of inpatient records was performed to ascertain this information approximately 24 hours following discharge from the PACU.

Twenty-four hours after discharge from the PACU, all subjects were interviewed (by phone or in person) to determine how satisfied they were with control of postoperative nausea and pain and their ability to concentrate. These areas of satisfaction were estimated by asking subjects to rate their postoperative experiences using a 1 to 5 satisfaction scale that included the following choices: 1, complete dissatisfaction (continuous severe pain; frequent nausea with vomiting; complete inability to concentrate); 2, dissatisfaction (frequent, severe pain; frequent, severe nausea; significant problems with ability to concentrate); 3, somewhat satisfied (moderate pain; moderate nausea; some difficulty with concentration); 4, satisfied (mild pain; minimal nausea; mild inability to concentrate); and 5, completely satisfied (no pain or nausea; complete resolution of ability to concentrate). The satisfaction scale was administered as 3 separate measurements, and the questions were tailored to reflect the area under question (pain, nausea and vomiting, ability to concentrate). In addition to collection of satisfaction data, subjects were asked to supply information about postoperative analgesic and antiemetic requirements. This was done by examination of a postoperative nausea and pain log that each subject was asked to keep for the first 24 hours following discharge. In this log, subjects noted the time and the name of the medication taken to treat nausea, pain, or both. The doses of analgesics taken after discharge from the PACU (to home or to an inpatient unit) were converted to morphine-equivalent doses for purposes of documentation on the data collection sheet.

Before initiation of the study, a power analysis was performed based on previous investigations that have used the NBMGT. When a probability level of .05 and power of 0.08 (1 – b) were used, it was determined that at least 4 missed dots with a SD of 6 missed dots would be required to detect a difference between groups. This yielded a sample size of 36 subjects needed in each arm of the study, and when a 15% attrition rate was factored into the calculation, it was determined that 42 subjects would be needed in each arm of the study.

Data analysis was accomplished using descriptive and inferential statistics and analyzed using the SPSS for Windows (Version 10.0, SPSS Inc, Chicago, Ill). Aldrete scores, demographics, and incidence of nausea and emesis were analyzed using the . Analyisis of the VNRS scores and performance on the sensory-motor performance test was accomplished using a 2-way repeated measures t test. All data are expressed as mean ± SD. A P value of less than .05 was considered significant.

**Results**

A total of 90 subjects were enrolled in this randomized investigation. Six subjects (3 in each group) were disenrolled for the following reasons: duration of surgery less than 2 hours (3 subjects), failure to follow the study protocol (1 subject), and laparoscopic procedure changed to open procedure (2 subjects), leaving a final sample of 84 subjects for analysis. Data analysis was not performed on data for subjects who were disenrolled from the study. Of 84 subjects, 42 were included in the thiopental group, and 42 were included in the propofol group. A total of 37 subjects required an overnight stay in the hospital, but no significant difference was noted between the thiopental (n = 21) and the propofol (n = 16) groups (P = .262). No differences in relation to age, sex, weight, or duration of anesthesia or surgery were noted between the groups (Table). No differences in admission or discharge Aldrete scores were noted between the groups.

When nausea was analyzed, no significant differences (P = .47) were noted overall between the groups in relation to the incidence of VNRS scores except at 105 minutes. At 105 minutes, a score of 1.60 ± 1.51 was noted in the thiopental group, compared with 0.14 ± 0.38 in the propofol group (P = .025) (Figure 2). Ten subjects in the thiopental group remained in the PACU for 105 minutes compared with 7 subjects in the propofol group, and of those 10 subjects, it also was noted that 4 subjects had emesis at this time. When the incidence of emesis was analyzed, it was noted that overall, 5 subjects in the thiopental group.
had emesis in the PACU compared with none in the propofol group \((P = .001)\).

Postoperative data for pain measured via the VNRS showed no statistical difference between the 2 groups at any interval measured. There also was no statistical difference \((P = .397)\) between groups when postoperative analgesic medication use (including morphine, meperidine, ketorolac, acetaminophen with codeine, and ibuprofen), measured in morphine equivalents, was compared.

Discharge times from the PACU and APD were analyzed and showed no statistical difference between the groups when postoperative recovery times were compared. Time to discharge from PACU was noted to be 88.21 ± 35.83 minutes for the thiopental group compared with 80.26 ± 32.76 minutes for the propofol group \((P = .304)\). Discharge times from the APD also were not significantly different between the thiopental (192.76 ± 75.18 minutes) and propofol (201.92 ± 78.33 minutes) groups \((P = .687)\) (Figure 3).

The NBMGT, which was used to assess recovery from anesthesia by measurement of psychomotor and visual acuity skills, was performed on all subjects at 15-minute intervals in the PACU and showed no significant differences \((P > .05)\) between the groups for any interval measured. The 3 NBMGT variables measured included number of dots missed, number of extraneous lines, and deviation from baseline. The only interval that approached statistical significance \((P = .046)\) was at 105 minutes, when subjects in the thiopental group missed 20.89 ± 9.65 dots compared with subjects in the propofol group, who missed 5.63 ± 11.2 dots (Figure 4). This decrease in reorientation in the thiopental group may be a reflection of synergism between analgesic and antiemetic treatment for continued pain and nausea in the PACU.

### Discussion

Based on the results of this study, propofol offers no advantages over thiopental in postoperative outcomes in laparoscopic surgical procedures longer than 2 hours. Although previous studies have demonstrated certain benefits to using propofol as an induction agent compared with thiopental, all of these studies
involved brief surgical procedures or had substantial flaws in the research design and method.

For example, Korttila et al\textsuperscript{21,24} performed a series of investigations that studied the recovery profiles of propofol vs thiopental. In 1992, they reported recovery profiles on 12 volunteers, all of whom received an IV induction dose of propofol or thiopental, then the subjects were allowed to recover from induction.\textsuperscript{21} Subjects were asked to perform tasks to measure psychomotor function at 1, 3, 5, and 7 hours.\textsuperscript{21} Korttila et al\textsuperscript{24} previously reported a comparison of the effects of propofol induction and continuous propofol infusion vs thiopental induction with isoflurane maintenance for 41 subjects.\textsuperscript{24} In both of these studies, Korttila et al\textsuperscript{21,24} reported that propofol was superior in both recovery and discharge times. In contrast with these studies, our study used actual surgical procedures and eliminated the confounding variable of having 2 separate induction agents and 2 separate maintenance agents. This allowed us to compare the effects of propofol and thiopental as induction agents only.

However, some studies reported no differences in postoperative outcomes between groups of patients induced with thiopental or propofol. For example, Ryom et al\textsuperscript{29} reported that there were no differences in recovery profiles in 80 subjects who underwent short laparoscopic procedures of roughly 20 minutes’ duration. Rashiq et al\textsuperscript{23} reported similar results in groups of patients who had undergone short laparoscopic procedures. The variables examined in these studies included incidence of nausea, vomiting, headache, and dizziness. However, subjects in the propofol groups were able to reorient significantly faster ($P > .05$) than subjects in the thiopental group, and this led directly to earlier discharge from the PACU.

The measurement tools used to analyze recovery were highly subjective, and no study used a tool as sensitive as the NBMGT. In addition, most of the studies did not comment on the length of surgery as one of the critical factors for determining postoperative outcomes. Because we believe that duration of the surgical procedure is an important element of any anesthetic, our study specifically measured the length of the surgical procedure as an important element of the research question.

Our study found no significant differences between propofol and thiopental induction when postoperative nausea, vomiting, antiemetic therapy, pain, pain therapy, recovery of coordination, and discharge to home were compared when the laparoscopic procedure was longer than 2 hours. The only timeframe in which an appreciable difference was noted between study groups occurred at 105 minutes, in which we found a higher incidence of nausea and vomiting in a small subgroup of patients given thiopental. Explanation for this finding at this specific timeframe cannot be explained by this study. Propofol may have provided some prophylaxis, but this study was not sensitive enough to determine the exact cause of this finding. An analysis of surgical procedure, surgical length, and opioid use (intraoperatively and postoperatively) failed to produce a significant difference between the groups in those subjects at 105 minutes. The only appreciable difference noted between the groups at the 105-minute timeframe was the increased requirement for ondansetron in subjects reporting nausea and emesis.

There were several limitations in our study. Foremost was the population under investigation. All subjects were active duty military personnel, military retirees, or military dependents. As such, this population’s health and healthcare experience may not be reflective of those of the general population. To determine whether our study groups differ significantly from the population as a whole, this study should be repeated at a civilian hospital in which the same type of surgical procedures are performed and using the same research design. It also should be noted that this study was performed in a training hospital for resident surgeons, and the length of surgeries and degree of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Comparisons of number of dots missed on Newman Bender Motor Gestalt Test (NBMGT) drawings (propofol vs thiopental groups)}
\end{figure}

\* Significance

The difference at the 105-minute mark was significant ($P = .046$). This was the only measurement at any interval that demonstrated a benefit for the propofol group and may have been due to synergism between analgesics and antiemetics given to the thiopental subjects for postoperative pain and nausea.
surgical manipulation and stimulus may be different from those in nontraining hospitals. Another parameter that we excluded from analysis involved individuals in which the laparoscopic procedures became open procedures. Perhaps if we had included those patients in the analysis, this small subgroup of subjects may have supported or refuted our findings. Another limitation of this study was the inability to blind the investigators to the induction agent used. While performance of a blinded study would have strengthened the research design, it is unlikely that a different outcome would have resulted, based on the findings. Finally, a large number of PACU nursing personnel were used to obtain data during the immediate postanesthesia period, and even though all PACU personnel were trained in the use of the data collection tool, completion required a diverse population of PACU personnel. Because of the diversity of personnel collecting data, a possibility of error introduction existed despite attempts to control for this by the extensive prestudy training of PACU personnel.

Cost containment is a growing concern in healthcare. Propofol has, in recent years, become the induction agent of choice for many anesthesia providers, regardless of the anesthetic duration. However, it is substantially more expensive than thiopental when equipotent doses are compared. Furthermore, because propofol has a recommended expiration of 6 hours once opened, it can account for substantial lost and wasted dollars. In one study, $80,000 worth of propofol was thrown away annually in partially full syringes. This is an important consideration because, in that study, the wastage associated with this one drug was as much as the loss and waste of all other drugs combined. Anesthesia providers, not surprisingly, are not blind to cost once the issue is introduced directly into the workplace. Lin and Miller placed the prices of medications directly on labels in the work cart and found that anesthesia providers made a conscious effort to use the less expensive medication if it was equally efficacious. Lower cost with equal efficacy is the strongest argument for selecting thiopental.

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