

Propofol Versus Thiopental — Isoflurane in Outpatient Surgical Procedures

Aaron Killian, Phillip Hamilton and Michael Tierney

ABSTRACT

The objective of this study was to assess the potential advantages of propofol to determine if it might be cost effective when compared with traditional anesthesia using thiopental and isoflurane (TI) for outpatient surgery. The study was designed as a prospective, randomized, biphasic trial (Phase I [peri-op]: single blind; Phase II [post-op]: double blind). Of 75 patients enrolled, 63 (33 propofol; 30 TI) had evaluable results. Patients were randomly assigned to receive induction and maintenance of anesthesia with either propofol or a combination of thiopental and isoflurane (TI). During recovery, the mean times to ambulation, tolerating liquids, and discharge were significantly lower in the propofol group. In addition, less direct patient care was required in the recovery room for those receiving propofol. Patients in the propofol group experienced less nausea and vomiting than those receiving TI. Patients regarded overall recovery from surgery to be significantly better with propofol. The average cost of propofol per patient (\$16.41) was approximately three times higher than with TI (\$5.45).

Key Words: anesthesia, isoflurane, propofol, thiopental

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RÉSUMÉ

On a effectué une étude prospective, aléatoire, biphasique (phase I [périopératoire]: à simple insue; phase II [post-opératoire]: à double insue) pour évaluer les avantages éventuels du propofol et déterminer si son emploi pour la chirurgie en unité de soins d'un jour est rentable, comparativement aux anesthésiques classiques, à savoir une combinaison de thiopental et d'isoflurane (TI). On a pu évaluer les résultats de 63 (33 propofols; 30 TI) des 75 patients qui ont participé à l'étude. Le choix des patients pour les deux types d'anesthésie s'est fait au hasard. Au réveil, les patients anesthésiés au propofol mettent, en moyenne, significativement moins de temps à marcher, à tolérer les liquides et à sortir de l'hôpital. De plus, ce groupe exige moins de soins dans la salle de réveil. Les patients anesthésiés au propofol ont moins de nausées et de vomissements que ceux anesthésiés avec le mélange thiopental-isoflurane. Dans l'ensemble, la récupération post-opératoire est nettement meilleure chez les patients anesthésiés au propofol. Le coût moyen par patient du propofol (16,41 \$) est environ trois fois plus élevé que celui de la combinaison thiopental-isoflurane (5,45 \$).

Mots clés: anesthésie, isoflurane, propofol, thiopental

Aaron Killian, B.S.P., Department of Pharmacy, Ottawa General Hospital
Phillip Hamilton, M.D., Department of Anesthesia, Ottawa General Hospital
Michael Tierney, M.Sc., Department of Pharmacy, Ottawa General Hospital

Address correspondence to: Michael Tierney, Department of Pharmacy, Ottawa General Hospital, 501 Smyth Rd., Ottawa, Ontario K1H 8L6.

INTRODUCTION

Propofol (2,6-diisopropylphenol), recently marketed by I.C.I. Pharma under the trade name Diprivan[®], is a new intravenous hypnotic agent shown to be effective for the induction and maintenance of anesthesia.¹

The pharmacokinetic properties² of propofol suggest it should allow a fast return of psychomotor function with a potential for rapid recovery and earlier discharge following outpatient procedures. Indeed, superior recovery after induction and maintenance with propofol when compared to thiopental

alone^{3,4} or combination anesthesia has been observed.⁵⁻⁷ Propofol has also been associated with a significant reduction in the incidence of nausea and vomiting⁷⁻⁹ which offers an improved quality of recovery.

Presently, a trend towards an increasing number of outpatient surgical procedures has been observed. Although the acquisition cost of propofol is currently more than traditional anesthesia, propofol has been associated with a more rapid recovery and a lower incidence of nausea and vomiting

than standard anesthetic agents. Thus, despite the costs associated with propofol, it may offer other economic benefits for the hospital and an improved quality of recovery for the patient.

Thus, the objective of this study was to assess these potential advantages of propofol (i.e., shortened post-anesthetic recovery (PAR) time and reduced nausea and vomiting) to determine the relative cost when compared with traditional anesthesia using thiopental and isoflurane for outpatient surgery.

METHODS

This study was a prospective, randomized biphasic trial. The perioperative, anesthetic administration segment (phase I) constituted the single blind phase during which the patient was unaware of the type of anesthetic regimen being given. The attending anesthesiologist, however, was fully cognizant of the type of anesthetic being used for each patient. The post-operative, recovery testing portion (phase II) was double-blind in nature as both the patient and the recovery room staff were unaware of the anesthetic regimen used in phase I.

Inclusion/Exclusion Criteria

Patients were eligible for the study only if ranked as ASA I or II based on the following classification devised by the American Society of Anesthesiologists:

- ASA I: healthy patient with localized pathological process
- ASA II: patient with mild to moderate systematic disease
- ASA III: patient with severe systemic disease limiting activity but not incapacitating
- ASA IV: patient with incapacitating systemic disease
- ASA V: moribund patient not expected to live

In addition, patients had to be scheduled for elective outpatient surgery and provide informed consent.

Patients were excluded if they were:

- 1) ASA category III, IV, or V
- 2) <18 or >65 years of age
- 3) pregnant or nursing mothers
- 4) suffered from disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, or pancreatitis
- 5) significant ischemic coronary artery disease or other cardiorespiratory insufficiency

- 6) significant hepatic or renal dysfunction
- 7) significant hematological abnormalities
- 8) malignant hyperthermia

Upon receiving permission of the Human Experimental Procedures Committee (HEPC), the study was carried out from May 28 to July 4, 1991 at the Ottawa General Hospital. Patients were randomly assigned to receive either propofol-NO₂ or thiopental-isoflurane-NO₂. The randomization was performed using a table of random numbers.

The induction sequence was left to the discretion of the attending anesthesiologist but did not vary significantly between groups. All but one patient from each arm of the study received 1.5 µg/kg fentanyl prior to induction (the other two patients received alfentanil). Succinylcholine, d-tubocurarine, and atracurium were used as necessary. The induction then followed, within three minutes, by either propofol 2.0-2.5 mg/kg (1% solution) or thiopental 4.0-5.0 mg/kg (2.5% solution) injected over 20-30 seconds. Maintenance of anesthesia

was initiated immediately thereafter by continuous administration of propofol (0.1-0.2 mg/kg/min) or isoflurane with the attempt to keep the amounts administered to a minimum (average endtidal concentration of 0.9%, free gas flow rate 3.1 mL/min). Both regimens were supplemented with nitrous oxide (60-70%) in oxygen. Anesthesia was stopped approximately five minutes before estimated surgery completion. Postoperative analgesia consisted of acetaminophen and codeine combinations. Analgesic use was not recorded.

Data Collection

From the time of surgery completion, the following parameters were recorded:

- 1) **Vitals** (BP, HR, RR, T°) — upon arrival to recovery room and every 15 minutes thereafter while in recovery
- 2) Time of **spontaneous eye opening**
- 3) **Modified Aldrete score** (Table I) — upon arrival to the recovery room and every 15 minutes until a score of 12 was achieved

Table I: Modified Aldrete Scoring Table

ACTIVITY	2 — moves all four extremities 1 — moves only two extremities 0 — no movement of extremities
RESPIRATION	2 — able to breathe easily/cough freely 1 — dyspnea/shallow or limited breathing 0 — apneic
CIRCULATION	2 — BP ± 20% pre-op level 1 — BP ± 20-50% pre-op level 0 — BP ± 50% pre-op level
	2 — HR ± 20% pre-op level 1 — HR ± 20-50% pre-op level 0 — HR ± 50% pre-op level
CONSCIOUSNESS	2 — fully awake 1 — arousable on calling 0 — not responding
COLOR	2 — normal 1 — pale, dusky, blotchy, jaundiced 0 — cyanotic
TOTAL SCORE	= x out of 12

4) Time to **orientation** — meaning time before patient responded correctly to the following:

What is your date of birth?

What is the name of this hospital?

What day of the week is it?

5) Unaided **sitting time**

6) Time to **tolerate 50 mL of clear liquid**

7) Time to **ambulation to bathroom for voiding**

8) Time to **discharge**

Psychomotor testing was performed on patients at baseline (pre-op) and on readmission to the short stay unit after surgery using the deletion of p's and ball bearing tests. For the deletion of p's test, patients were instructed to delete as many p's as possible in 60 seconds working left to right in a column of closely packed letters. One point was scored for each p deleted while one and two points were deducted for omitting a letter p or deleting a letter other than p, respectively. In the bead transfer test, patients were given one point for each bead transferred (via forceps) from a tray of beads into a 12 inch graduated cylinder within 40 seconds. For both tests, the patient was instructed to work as quickly as possible.

In addition, the amount of direct nursing care required by all patients in the recovery room was tabulated for comparison between groups. This information is routinely collected by nursing as part of their workload measurement system.

The number of episodes of nausea/emesis as well as the number and type of antiemetics administered were recorded for each patient following surgery.

After being deemed suitable for discharge, a questionnaire was completed by each patient to serve as a personal, subjective assessment of the surgical procedure.

The drug costs of the two anes-

thetic regimens were calculated for each patient based on (1) the total amount of anesthetic used in surgery (x wholesale cost of anesthetic(s)), and (2) the total amount of antiemetic(s) used post-op (x wholesale cost of antiemetic(s)). As both groups received muscle relaxants at the discretion of the anesthesiologist, these costs were not included in the analysis.

Statistical Analysis

Frequency data for patient sex and the number of patients experiencing nausea and emesis were analyzed by the Yates' corrected Chi-square test while the total number of episodes of vomiting was evaluated using the Wilcoxon Rank Sum test. Data from psychomotor testing were analyzed using the Wilcoxon Sign Rank test using the baseline score for comparison. All other data were analyzed using the Student's and Welch's t-tests where appropriate. Results are presented as mean \pm standard error.

RESULTS

Demographic data were presented in Table II. Both groups were comparable with respect to age, sex, type of surgery, and duration of surgery. Of the 75 patients enrolled in the study, 12 were excluded (propofol=8, thiopental-isoflurane (TI)=4): six patients did not have data recorded (propofol=5, TI=1), two were too young (propofol=2), one had severe asthma (propofol),

one received enflurane instead of isoflurane (TI), one received pre-induction droperidol IV (TI), and one patient's stay in the recovery room was prolonged for two hours because the short stay unit was full (propofol). Thus, a total of 63 patients were included for statistical analyses (propofol=33, TI=30).

The times to spontaneous eye opening, correct responses for orientation, and unaided sitting were slightly, though not significantly, lower in the propofol group. The time to achieve a mean Aldrete score of 12 was identical in both groups. The mean amount of direct patient care required for each patient in the recovery room was significantly lower for patients receiving propofol (31.2 ± 1.2 vs. 37.2 ± 2.0 minutes, $p < 0.02$). Patients ambulated to the bathroom (112 ± 5.2 minutes vs. 142 ± 9.4 minutes) and tolerated fluids (71 ± 3.6 vs. 101 ± 9.2 minutes) earlier following propofol anesthesia ($p < 0.01$ for both). On average, subjects were deemed suitable for discharge approximately one-half hour earlier (134 ± 6.6 vs. 163 ± 9.3 minutes) if they received propofol as opposed to TI ($0.01 < p < 0.02$). Table III summarizes the times for the various parameters outlined above.

Due to time constraints, psychomotor testing was only performed on the first 28 patients (14 propofol, 14 TI). A decline in psychomotor functioning was seen in both treatment groups compared to

Table II: Demographic Data

	Propofol (n=33)	TI (n=30)
1) Patient		
a) age (years)	32 ± 1.8	36 ± 2.5
b) sex (F/M)	25/8	24/6
2) Type of procedure		
a) gynecological/laparoscopy	17	17
b) orthopedic	11	8
c) other	5	5
3) Procedure duration (minutes)	39 ± 3.1	41 ± 4.4

Table III: Recovery Times (minutes)

	Propofol	TI	p
	(n=33)	(n=30)	
Spontaneous eye opening	8.4 ± 1.3	8.7 ± 1.3	>0.4
Correct orientation responses	14.9 ± 2.1	15.4 ± 1.8	>0.4
Aldrete score of 12	13 ± 2.0	13 ± 1.9	>0.4
Ambulation to bathroom	112 ± 5.2	142 ± 9.4	<0.01*
Discharge	134 ± 6.6	163 ± 9.3	<0.02*
Direct patient care	31.2 ± 1.2	37.2 ± 2.0	0.01<p<0.02*
	(n=23)	(n=20)	
Unaided sitting	53 ± 8.9	74 ± 12	0.1<p<0.2
	(n=32)	(n=27)	
Tolerate clear fluids	71 ± 3.6	101 ± 9.2	<0.01*

*p<0.05

Table IV: Patient Questionnaire Responses

	Propofol	TI	p
	(n=33)	(n=29)	
Groggy feeling/unable to concentrate	1.70 ± 0.14	1.97 ± 0.16	0.2<p<0.4
Loss of memory	1.00 ± 0.00	1.10 ± 0.08	>0.4
Nausea	1.36 ± 0.14	1.66 ± 0.15	0.1<p<0.2
Vomiting	1.36 ± 0.16	1.52 ± 0.16	>0.4
Overall recovery	4.55 ± 0.11	3.97 ± 0.16	<0.01*
	(n=23)	(n=16)	
Comparison to previous surgery	4.35 ± 0.20	4.44 ± 0.16	>0.4

*p<0.05

baseline testing. The average decrease was -2 ± 1.8 and -3 ± 1.5 (deletion of p's) and -2 ± 1.1 and -1.1 ± 0.9 (ball bearing) for the propofol and TI groups, respectively (propofol=14, TI=14). The only statistically significant difference was with the deletion of p's test in the TI group ($p=0.05$).

Nausea was significantly lower (propofol=5 [15%], TI=15 [50%]) in the propofol group ($p=0.0066$). There were 29 episodes of vomiting (propofol=7, TI=22) in 15 different patients (propofol=5, TI=10). However, neither the number of patients experiencing vomiting ($p=0.1392$) nor the total number of episodes ($0.1<p<0.2$) were statistically different between the two arms of the study.

Patient questionnaires revealed significantly superior "overall recovery" scores ($p<0.01$) for subjects assigned to propofol ($4.55 \pm$

0.11) as compared to TI (3.97 ± 0.16). In general, subjects reported only mild concentration deficits, memory loss, nausea, and vomiting. These scores were slightly, but not significantly, lower in propofol treated patients. Likewise, when asked to compare recovery following this surgery to past surgical procedure(s), no difference was observed between the anesthetics. The majority reported recovery as being mildly or much better than in the past regardless of which anesthetic regimen they received. Table IV provides the mean scores for each group.

The mean propofol dose per procedure was 399.3 mg which translates into a drug acquisition cost of \$16.41. The mean dose and acquisition cost for thiopental were 309.3 mg and \$0.83, respectively. The mean dose and acquisition cost for isoflurane were 5.8 mL and

\$4.61, respectively. Therefore, a three-fold difference in the mean anesthetic cost per patient between the two regimens (propofol \$16.41, thiopental-isoflurane (TI) \$5.45) was calculated. A total of 12 antiemetics (propofol=3, TI=9) were used in ten subjects (propofol=3, TI=7) for a total cost of \$1.20 and \$42.02 in the propofol and TI groups, respectively. The number of patients requiring antiemetics did not differ significantly between groups. The higher cost of antiemetics in the TI group was due to the fact that droperidol was only used in this group (total of four ampoules used).

DISCUSSION

For an average 40 minute outpatient surgery, the cost of propofol anesthesia is roughly three times that of TI. As our cost calculations were based on amount of drug administered, any drug wastage would tend to magnify the cost differences between propofol and TI. The incidence of nausea was significantly greater with TI but, the number of patients requiring medication to control emesis was not significantly different between propofol and TI treated patients.

Subjectively, patients receiving propofol reported significantly higher overall recovery scores. Objectively, propofol recipients tended to recover faster based on time to tolerate clear fluids, as well as ambulation and discharge times. Psychomotor functioning, as assessed by the deletion of p's test, declined significantly only in the TI group. It is possible that a larger sample size would have produced more significant differences between the groups.

Based on acquisition cost alone, TI would be the preferred agent for such outpatient surgical procedures. However, other factors must also be taken into consideration.

Antiemetic usage was compar-

able between groups and, thus, should not play a major role in determining the overall cost of the anesthetic regimens. In this study, the cost was higher in the TI arm. This was a direct result of the high cost of droperidol which was used exclusively in the TI group. As we did not control antiemetic prescribing, it is not known if the use of droperidol was warranted in the TI group. If a less expensive antiemetic (e.g., dimenhydrinate) had been administered to these patients, the cost differential would have been negligible. Other factors such as cost of propofol infusion pumps, personnel training for proper propofol administration, drug wastage, syringes, tubing, and other accessory costs were not examined, but, nonetheless, are important considerations for any given institution.

Quality of recovery is a key element in determining a suitable anesthetic regimen. The outpatient surgery questionnaire was designed to subjectively assess this parameter. The findings suggest a very acceptable recovery regardless of the type of anesthetic used and a significantly better overall recovery with propofol. Improvements in anesthetic techniques may have been the reason for a marked preference of this surgery over previous procedure(s) regardless of which anesthetic was received.

Recovery was assessed objectively with both the deletion of p's and bead transfer tests. These tests were chosen based on the assumption that the deletion of p's test would more accurately assess cognitive function while the bead transfer test would be a better indicator of motor capability. Unfortunately, due to the time-consuming nature of the psychomotor testing, these tests were only performed in the first 28 patients (propofol=14, TI=14).

No difference was reported in

time to spontaneous eye opening, correct responses for orientation, unaided sitting, and attainment of a modified Aldrete score of 12. One problem with these parameters, however, is that they occur within a short time frame upon admission of the patient to the recovery room. For example, since the nurse to patient ratio is less than 1:1, the recording of a parameter such as spontaneous eye opening may actually be delayed when the recovery room is full and the nurse:patient ratio is at a minimum. Thus, it is relatively easy to record an incorrect time which may affect the validity of the data. Furthermore, specific surgical procedures can affect response times in a given patient (e.g. ability to sit following a laparoscopy, ambulation following arthroscopy of the knee).

The discharge time in our study was defined as the time that the patient was deemed ready to leave and not when the patient actually left the unit. One factor which may have affected our results is that the time a patient is deemed ready for discharge may vary from one nurse to the next. Ideally, this should be performed by only one blinded observer so that there is consistency in the recorded times.

Previous studies by Herregods¹⁰ and Zuurmond¹¹ were reviewed to determine the average maintenance cost of propofol versus isoflurane.¹² The cost differential in both studies correlates well with our findings taking into consideration the longer duration of anesthesia and subsequently higher anesthetic doses administered for each study.

The economic analysis of propofol compared to TI has also been reported based on retrospective data interpretation¹³ where PAR was broken down into two phases. Phase I began at the end of surgery and continued until an Aldrete score of 10 was achieved. Phase

II then started immediately and ended when the patient was ready for discharge. Significant reductions in PAR were noted for both phases of the study. Based on a switch from a hypothetical 100% TI regimen to a 100% propofol regimen, it was estimated that the number of hours of direct patient care was reduced, and the recovery room staffing could be decreased by approximately 25%.

In another study, propofol was compared to TI in 99 ASA class I-III individuals. Patients receiving propofol had significantly less nausea, direct nursing care, and returned to work earlier than those given TI.¹⁴ It was estimated that in a 4,000 case/year facility, 1,000 nursing hours would be saved since patients given propofol required 15 minutes less time in phase I recovery.

In contrast, our study revealed no significant difference in phase I PAR (using a modified Aldrete score of 12) but a greater reduction in phase II PAR. Two important findings were the lower incidence of nausea and the faster discharge times associated with propofol. These would reduce the amount of direct patient care required at our institution. This was confirmed by the fact that patients given propofol required less direct care by the recovery room nurses in our study.

It would seem that propofol would be most cost effective in an outpatient setting where it would be utilized for all cases requiring general anesthesia. This would make it more feasible to reduce nursing staff and/or perform more surgeries on a daily basis. In this manner, nursing hours could be reduced in advance knowing that there would be a relatively constant nursing demand on a daily basis. Otherwise, with sporadic use of propofol, nursing staff would still have to be sufficient to cover for such fluctuations, and the total out-

patient surgery expense may be increased.

In conclusion, propofol anesthesia for outpatient surgical procedures is associated with higher drug acquisition costs than traditional anesthesia. It is, however, associated with an improved PAR time and quality of recovery for the patient. The economic benefits of propofol are most likely to be seen in outpatient clinics with a large nursing staff and a high patient volume per day where a significant reduction in nursing staff could be undertaken. Smaller institutions with modest nursing staff would be least likely to benefit as it would be more difficult to reduce recovery room staffing. 

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