Revista Mexicana de Anestesiología

Volumen *Volume* **28** **Número** *Number* **1** **Enero. Marzo** *January-March* **2005**

Artículo:

Total intravenous Anesthesia with Propofol and Fentanyl: A Comparison of Target-Controlled *versus* Manual Controlled Infusion Systems

Revista Mexicana de Anestesiología

ARTÍCULO ORIGINAL
Vol. 28. No. 1 Enero-Marzo 2005
pp 20-26

Total Intravenous Anesthesia with Propofol and Fentanyl: A Comparison of Target-Controlled *versus* Manual Controlled Infusion Systems

Dr. Gustavo Lugo-Goytia,* Dr. Víctor Esquivel,** Dr. Hilario Gutiérrez,*
Dr. Antonio Hernández-Rayón*

* Professor of Anesthesiology.
** Department of Anesthesiology, Hospital General "Dr. Manuel Gea González". México D.F., México.

Correspondence and reprints:
Dr. Gustavo Lugo Goytia
Hospital General "Dr. Manuel Gea González"
Calzada de Tlalpan 4800, C.P. 14000,
México, D.F., México
FAX: 55 28 17 47
e-mail: lugogoy@yahoo.com.mx

Recibido para publicación: 06-07-04
Aceptado para publicación: 23-08-04

SUMMARY

This study was designed to compare the clinical performance of an effect-site target-controlled infusion (TCI) system versus a manually controlled infusion (MCI) system in 19 ASA I/II patients undergoing laparoscopic surgery. Patients were randomly assigned to receive TIVA with propofol by either a MCI or TCI system. Besides propofol, patients in both groups received a continuous fentanyl infusion to maintain a constant target concentration of 1.5 ng/ml. Propofol infusion rate or propofol target effect-site concentration were titrated to maintain an adequate anesthetic depth, defined as mean arterial pressure and heart rate within 20% of baseline values, plus absence of somatic and autonomic signs. Use of TCI resulted in more rapid induction of anesthesia, but requiring significantly greater propofol doses. However, the overall rate of propofol administration was significantly lower with the TCI system. Superior hemodynamic control was achieved with the TCI than with the MCI system. Times to eye opening and orientation were slightly but significantly shorter in the TCI group. Control over the depth of anesthesia was easier and more precise with the TCI system. The time for patients to fulfill the criteria for discharge from the PACU was similar with both systems. It is concluded that both systems provided acceptable clinical anesthetic conditions, with a rapid and predictable recovery. However, an effect-site TCI system offers the advantage of an easier and more precise control to modify the depth of anesthesia, better hemodynamic stability, and a slight reduction in overall propofol consumption.

Key words: Anesthetics, intravenous, propofol, target-controlled infusion, manual infusion, effect-site compartment, laparoscopic surgery.

RESUMEN

Este estudio fue diseñado con el propósito de comparar el desempeño de un sistema de infusión automatizado con control de concentraciones objetivo (TCI) versus un sistema de infusión controlado manualmente (MCI) en noventa pacientes con estado físico I/II sometidos a cirugía laparoscópica. Los pacientes fueron asignados aleatoriamente a recibir ATIV con propofol utilizando un sistema TCI o MCI. Además de propofol los pacientes de ambos grupos recibieron una infusión continua de fentanyl para mantener una concentración objetivo de 1.5 ng/ml. La velocidad de infusión de propofol o la concentración objetivo en sitio efector fue ajustada para mantener una adecuada profundidad anestésica, definida como una presión arterial media y una frecuencia cardíaca dentro de un 20% de los valores basales y ausencia de signos somáticos o autonómicos. El uso de TCI resultó en una más rápida

inducción de la anestesia a expensas de una dosis significativamente mayor de propofol. Sin embargo, la cantidad total de propofol administrada durante el procedimiento fue significativamente menor con TCI. Un mejor control hemodinámico se logró con el sistema TCI. Los tiempos de apertura ocular y orientación fueron significativamente más cortos para el sistema TCI. El control sobre la profundidad anestésica fue más fácil y más preciso con el sistema TCI. El tiempo para alcanzar los criterios de alta fue similar en los dos grupos. Concluimos que ambos sistemas proveen condiciones anestésicas aceptables con una recuperación rápida y predecible. Sin embargo, un sistema TCI ofrece la ventaja de un control más fácil y preciso para modificar la profundidad anestésica, mayor estabilidad hemodinámica y discreta reducción en el consumo total de propofol.

Palabras clave: *Anestésico, intravenoso, propofol, infusión controlada automatizada, infusión manual, cirugía laparoscópica.*

INTRODUCTION

The development of new short-acting intravenous anesthetics with a more suitable pharmacokinetic and pharmacodynamic profile and the introduction of novel drug delivery systems has increased the practice of total intravenous anesthesia (TIVA).

Recently, Target Infusion (TCI) systems has been developed to provide improved convenience and control during TIVA. TCI is an infusion system which allows to select the blood concentration required for a particular effect, and then to control the depth of anesthesia by adjusting the request target concentration using a computer with a population pharmacokinetic model to control an infusion pump. Several potential benefits of TCI over manually controlled infusion (MCI) has been claimed by some investigators[1,2], and the predictive accuracy of TCI systems for several anaesthetic drugs has recently been reported[3-5].

The effect site is the theoretical compartment in which a drug exerts its action, and the concentration at this site is a direct determinant of a drug´s effect. Hence, it is expected that targeting effect site concentrations could improve the clinical performance of an infusion system. Nevertheless, the studies performed so far has been designed to control plasma concentrations[6-9], and there are no published reports on the clinical performance of a TCI system targeting and controlling the effect site concentrations.

The objective of this study was to compare the clinical performance of an effect site target controlled infusion (TCI) versus a manual controlled infusion (MCI) system in ninety ASA physical status I/II patients undergoing laparoscopic surgery.

METHODS

After obtaining institutional review board approval and informed consent, 90 American Society Anesthesiologist (ASA) physical status I or II patients scheduled to undergo laparoscopic procedures expected to last at least 1 hour were enrolled in this study. Patients were randomly assigned to receive continuous intravenous (IV) propofol by either an MCI or a TCI system. Patients with known neurologic disease and with cardiovascular, respiratory or metabolic diseases, impaired renal or hepatic function, evidence of morbid obesity as defined by a body mass index > 35, Mallampati > 2, or a history of alcohol or drug abuse were excluded from participating in this study.

Patients were not randomized until 1 hour prior to the surgery when sealed randomized envelopes were opened to reveal the treatment assigned to each patient. On arrival in the operating room, intravenous catheters were placed, as were electrocardiogram leads, non invasive pressure recordes, capnometer, and pulse oxymeter. Preoperative medications were administered at the discretion of the anaesthesiologist and included 10 mg intravenous (IV) metoclopramide, ranitidine 50 mg IV, and midazolam 20 μg/kg, given shortly before induction of anesthesia. Before induction of anesthesia, patients breathed 100% oxygen for 3 min and were given 500 ml intravenous lactated Ringer´s solution. At induction of anesthesia, the MCI system delivered a propofol infusion at a rate of 1,200 ml/h until loss of consciousness as defined by loss of eyelid reflex and verbal contact, and then was maintained by a three step infusion as suggested by Vuyk et al[10]. The TCI system was set to reach a propofol target concentration of 3.5 to 4.0 μg/ml in the effect site. At induction, all the patients (TCI and MCI) also received a fentanyl infusion designed to maintain an effect site concentration of 1.5 ng/ml. Thereafter, vecuronium, 100 μg/kg, IV bolus, was administered to provide muscle relaxation, and the patient´s trachea was intubated. The patient´s lungs were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 28 to 32 mmHg. No additional doses of vecuronium were given. Muscle relaxation was monitored with a train- of- four nerve stimulator.

TCI was implemented by using a Harvard 22 electronic syringe pump (Harvard Apparatus, S. Natick, M.A.) driven by a RS232 link from an IBM compatible computer. The pump was controlled by the STANPUMP* pharmacokinetic software model and control system. Briefly, the system used a multi-compartimental kinetic model to predict plasma and effect site concentrations of drugs and adjust the rate of infusion to maintain a pre-set predicted plasma or effect site concentration. The pharmacokinetic parameters used in this study for propofol; Vc = 0.350 l/kg, k_{10} = 0.0889 min^{-1}, k_{12} = 0.0621 min^{-1} k_{21} = 0.0108 min^{-1}, k_{eo} = 0.250 min^{-1}, were based on the data of Shaffer included in STANPUMP*. The pharma cokinetic parameters used for fentanyl, Vc = 0.269 l/kg, K_{10} = 0.0410 min^{-1}, k_{12} = 0.1850 min_{-1}, k_{13} =0.1410 min^{-1}, k_{21} =0.1030 min^{-1}, k_{31} =0.0200 min^{-1}, k_{eo} =0.147 min^{-1}, were obtained from McClain and Hugh included in STANPUMP*. Propofol and fentanyl were infused separately and independently into an intravenous catheter.

During surgery, propofol target concentrations or infusion rates were increased or decreased according to individual anesthetic course. If patients exhibited signs of inadequate anesthesia indicated by movement, swallowing, tearing, sweating, an increase in mean arterial blood pressure or heart rate of more than 20% above baseline values, targeted propofol concentrations or infusion rates were increased. To increase propofol concentration in the MCI group, a bolus dose of 250 μg/kg was given, if the response was not controlled, a second bolus dose followed by an increase in infusion rate of 10 μg/kg/min was delivered. To increase propofol concentrations in the TCI group, the target concentration was raised by 0.5 μg/ml. The average number of actions on the anesthesia administration device was defined in the TCI group by the number of target concentration modifications and in the manual group by the number of infusion rate modifications and the number of bolus administrations needed to control somatic and/or hemodynamic responses. Intermittent non-invasive BP and HR were recorded following specific stimuli and at 5 minute intervals, using an automated blood pressure recorder. Descriptions of all important introperative events, including all episodes of inadequate anesthesia, were recorded.

Fentanyl infusion was stopped 10 minutes before the end of surgery in all patients. Residual muscular block was antagonized at the end of the operation in those patients who showed incomplete recovery of the neuromuscular function. Reversal of residual neuromuscular block was obtained with the administration of intravenous atropine (20 μg/kg) and neostigmine (50 μg/kg). Thereafter, oxygenation was maintained by intermittent positive ventilation with 100% oxygen until the return of spontaneous respiration. Once spontaneous ventilation was established, if the end-tidal carbon dioxide partial pressure was less than 45 mmHg, tidal volume more than 7 ml/kg, and respiratory rate more than 12 breaths/min, the trachea was extubated. Propofol administration was discontinued at the end of surgery and this moment was identified as the starting point of patient recovery. To reproducibly assess emergence time, the patient was asked in a normal tone of voice by an independent observer to open his or her eyes. This was repeated every minute until an appropriate response was obtained. The patients were then asked to give their name and date of birth every minute after tracheal extubation until a positive response was obtained. The time required for the patients to fulfil recovery room discharge conditions (Pulse and mean blood pressure $\pm$ 20% baseline; respiratory rate 12-24; O_2 saturation > 90%; temperature > 35.5°C orally; alert and oriented; no current vomiting; pain none to moderate) was also evaluated by a blinded observer.

Descriptive statistics were used to characterize demographic variables of each of the study groups. Comparisons between treatment groups were conducted using either the chi-square test, fishers exact test, Mann-Whitney U test, Student´s t-test, or analysis of variance for repeated measurements followed by t-test with Bonferroni correction. Data are displayed as mean $\pm$ SD, with P values < 0.05 considered statistically significant.

The sample size calculation was based on the primary end point of total propofol consumption. Based in previous studies we expected that the patients controlled with a MCI system would receive a total propofol dose of 140 $\pm$ 20 µg/kg/min. Based in this information we determined that a sample size of 40 patients per group would permit to detect a 20% reduction in propofol consumption in the TCI group with a 10% probability for a type II error (power of 90%) and with a probability for type I error of 5%[11]. A final sample size of 45 patients per group was decided to allow for possible participant attrition.

RESULTS

As shown in table I there were no significant differences among the groups regarding ASA class, age, gender, weight, surgery type, duration of surgery, and premedication.

Induction of anesthesia was achieved significantly more rapidly in the patients that received the TCI system, at the expense of significantly greater propofol dose. However, the overall rate of propofol administration was lower with the TCI system. As directed by the study design, no differences were detected regarding the fentanyl requirements in both groups (Table II).

Figures 1 and 2 shown the changes in mean arterial pressure and heart rate, expressed as percentage of basal values at selected time points, and the coefficients of variation dur-

ing maintenance of anesthesia, respectively. At induction, there was significantly reduction in MAP and HR in both groups with respect to baseline values. However, the difference between groups was not significantly. At intubation, MAP and HR increased toward baseline values in both groups. The increase in MAP and HR, was significantly higher with the MCI system. During the intraoperative period the coefficients of variation for MAP and HR were lower with the TCI system (Figures 3 and 4).

The time required for eye opening and orientation was also significantly shorter in the TCI group compared with the MCI group. The time for the patients fit the criteria for discharge from the PACU was similar with both systems (Table III).

Table IV shows the mean number of actions on the device and the number of patients that presented 0, 1, 2, or ≥ 3 somatic responses during the intraoperative period. The number of actions on the device was significantly greater wihen the MCI system was used. The somatic response, defined as movement or bucking, was greater with the MCI system. The time with 2 or more train-of-four responses was not different between the groups (MC, 87$\pm$ 17 *vs* TCI, 81 $\pm$ 15 min).

The calculated effect site concentrations of propofol and fentanyl at which patients in the TCI and MCI groups opened their eyes and responded to simple questions were not significantly different (Table V).

Table I. Patients demographic and clinical data.*

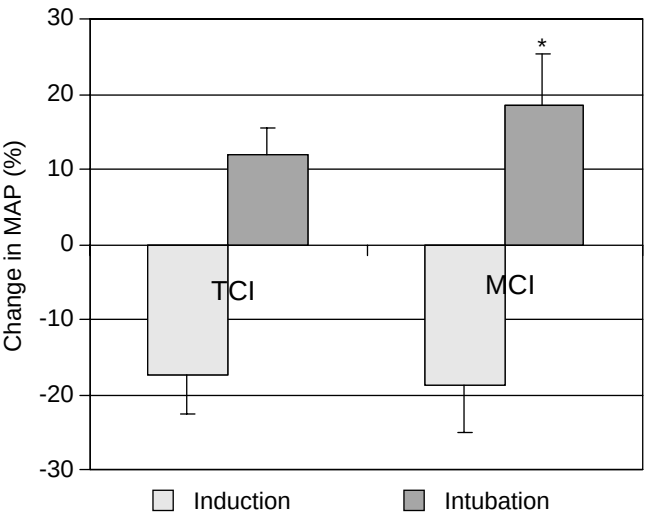
	MCI	TCI
No. of patients	45	45
Males/females	3/42	5/40
Age (yr)	39 ± 7	37 ± 9
Weight (kg)	64.1 ± 11.2	67.9 ± 12.9
ASA Physical status (I/II)	36/9	37/8
Surgery type (n)		
Cholecystectomy	35	34
Hysterectomy	10	11
Premedication		
Metoclopramide	42	43
Ranitidine	42	43
Midazolam	45	45
Total duration of anesthesia (min)	158 ± 45	166 ± 401

* There were no significant differences between the two groups.

Table II. Induction time and intraoperative propofol and fentanyl consumption.

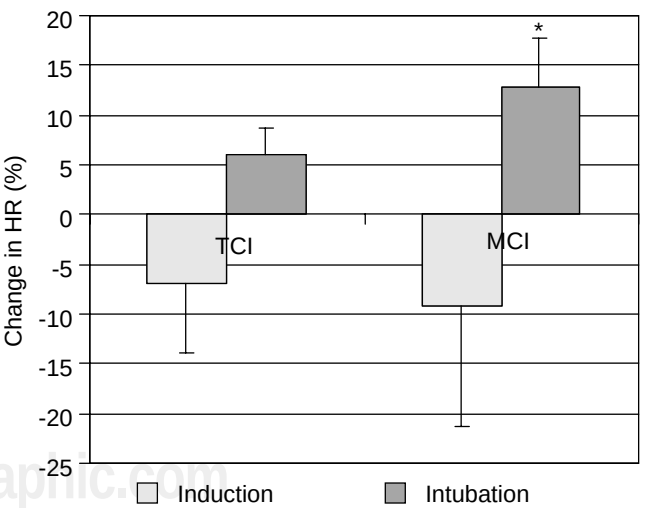
	MCI	TCI
Induction time (s)	77 ± 17	54 ± 13[a]
Propofol induction dose (μg/kg)	1.8 ± 0.5	2.4 ± 0.3[a]
Propofol infusion rate (μ. kg^{-1}.min^{-1})	134.7 ± 12.1	118.8 ± 7.7
Fentanyl infusion rate (μ. kg^{-1}.min^{-1})	0.057 ± 0.008	0.057 ± 0.009

[a] p < 0.05 by unpaired t test



* p < 0.05 by ANOVA

Figure 1. Change in mean arterial pressure expressed as percentage of basal values at induction and intubation.



* p < 0.05 by ANOVA

Figure 2. Change in heart rate expressed as percentage of basal values at induction and intubation.

DISCUSSION

Clinical studies which compare TCI *versus* MCI systems has been designed to control plasma concentrations[6-9]. However, it is known that concentrations in the effect site (biophase) rather than plasma concentrations, are a direct determinant of drugs effect. Therefore, it was hypothesized that targeting concentrations at the effect site could lead to a better control of anesthetic course and reduce propofol consumption. Our results showed that both systems provided excellent clinical anesthetic conditions with a rapid and predictable recovery. However, an effect site TCI system offers an easier and more precise control to modify the anesthetic depth, and a reduction in overall propofol consumption.

Table III. Time needed to achieve the recovery endpoints for manual and TCI groups.

Recovery endpoint	MCI	TCI
No. of patients	45	45
Open eyes (min)	12.7 ± 5.2	7.2 ± 2.7[a]
Respond to commands (min)	16.0 ± 4.1	11.4 ± 3.0[a]
Elegible for discharge (min)	75 ± 12	72 ± 11

[a] $p < 0.05$ by unpaired t test.

Table IV. Mean number of action on the device and number of patients with 0, 1, 2, or ≥ 3 somatic responses with the MCI and TCI systems.

	MCI	TCI
Actions on the device	7.3 ± 3.0	3.1 ± 1.6[a]
Number of somatic responses		
0	16	28b
1	21	14
2	5	3
≥3	3	0

[a] $p < 0.05$ by Mann- Whitney U test
[b] $p < 0.05$ by χ^2 test (0 responses *vs* 1, 2, and ≥ 3)

Table V. The calculated effect site concentration of propofol and fentanyl at which patients in the TCI and MCI groups opened the eyes and respond to simple questions.*

	TCI	MCI
Propofol (μg/ml)	45	45
Open eyes	1.32 ± 0.45	1.29 ± 0.50
Respond questions	0.82 ± 0.21	0.85 ± 0.37
Fentanyl (ng/ml)		
Open eyes	1.05 ± 0.03	1.09 ± 0.04
Respond questions	0.95 ± 0.05	0.93 ± 0.03

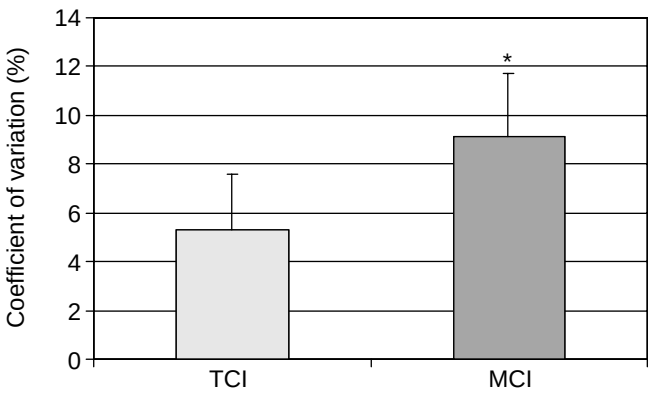
* There were no significant difference between the groups.

In view that the plasma is not the site of drug effect for drugs used to maintain the anesthetic statge, titration of plasma concentrations may not necessarily translate into precise control of drug effect. Hence, the anesthesiologist targeting the plasma would not be able to track with precision the rapid changes in the intensity of the surgical simulation, and therefore an "overdose" is more likely to occur. This problem relates to the slow equilibration of propofol with the brain. Schuttler et al[12] reported a blood-brain equilibrium half time for propofol in humans of approximately three minutes, and Peacock et al[13] showed that there is a prolonged disequilibrium between the arterial and jugular venous concentrations of propofol in humans during the induction of anesthesia. Therefore, titration to effect using a MCI system is more likely to be associated with an excessive of propofol.

Transient higher concentrations of propofol may explain the greater hemodynamic variability during the intraoperative period. A direct effect of propofol on vascular smooth muscle in addition to myocardial depression has been proposed to explain the reduction in arterial pressure associated with the induction of anesthesia[14,15]; therefore, higher concentrations in the blood may influence the degree of hemodynamic stability. Also the desequilibrium between the arterial and cerebral concentrations make it more difficult to titrate to effect using a MCI system, which explains the higher incidence noted in the somatic responses and actions taken to maintain an adequate depth of anesthesia. Therefore, our data support the additional clinical benefit of a TCI system when the effect site is targeted, and suggest that the integration of an effect site compartment in the pharmacokinetic algorithm of a TCI commercial system could permit a more accurate control of anesthetic conditions and recovery.

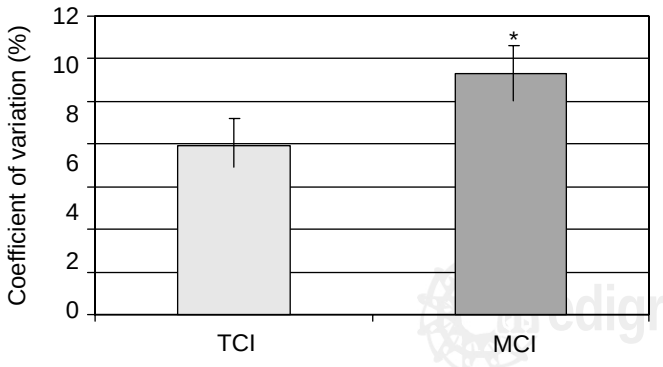
The TCI and MCI systems have been compared clinically. Russell et al[6] have shown in patients undergoing surface procedures with a duration between 20 and 60 minutes that the TCI system was similar to the MCI system in respect to the anaesthetic conditions and recovery times. However, propofol consumption was significantly higher in the TCI group than the MCI group. More recently, Servin[7] compare the clinical profile of "Diprifusor" TCI *versus* MCI systems in a multicentre study that included 565 patients, aged 18-25 years, undergoing surgical procedures ranged from ambulatory surgery to intra-abdominal or neurosurgical procedures. Their results showed that the overall rate of propofol administration was

slightly higher, and that the times to eye opening and orientation were significantly longer in the TCI group than in the MCI group. In contrast our data showed shorter recovery times and lower propofol consumption in the TCI group as compared with the MCI group. These differences may be related with the type and duration of surgery, characteristics of the patient population, and the pharmacokinetic model included in the TCI system. The study design was also different because our protocol permitted the anesthesiologist to titrate the concentrations according to objective criteria, while the target fentanyl concentration was controlled in both groups. In addition, in the study by Russell et al[6] the patients were anaesthetized by eight consultant anaesthetists who had little or no previous experience in the use of propofol by infusion. In the Servin´s[7] study the anesthetist had previous experience of manual infusion techniques for delivery of propofol but TCI was a new technique for most of them and therefore, it is pressumed that they did not titrate the target concentrations to the patient response, as efficiently as, they would usually do with manual infusions. This represent a bias toward a better performance of the MCI system. In our study, both systems were controlled by only two investigators with extensive experience in TCI and MCI techniques. This data suggest that the clinical profile of TCI is sensitive to the experience of the anesthetists, and therefore, it is expected that its performance will be improved as its clinical use increase.



* p < 0.05 by unpaired t test.

Figure 3. Comparison of coefficient of variation in mean arterial pressure during maintenance of anesthesia.



* p < 0.05 by unpaired t test

Figure 4. Comparison of coefficient of variation in heart rate during maintenance of anesthesia.

Previous studies have shown different results about the dose requirements during anesthetic induction. Russell et al[6] showed a greater propofol consumption at induction of anesthesia and more rapid loss of consciousness (loss of verbal contact) with a TCI system. However, their results differ from those obtained by Servin[7] in a multicentric study, which showed a lower dose and a longer induction time with the use of a TCI system. Their study design, characteristics of patients populations, premedication, surgical procedures, and experience in the use of a TCI system by the participant anesthesiologist can be important factors to explain the difference in results. In our patients a more rapid induction of anesthesia was achieved with the TCI system. However, this earlier loss of consciousness was obtained at the expenses of significantly increased propofol consumption. This should be explained because to obtain a rapid target effect site concentrations it is required the establishment of increased concentration gradient between plasma and biophase[15], a similar concept to that of overpressure used with inhalation anesthesia. However, despite a greater propofol induction dose the degree of cardiovascular depression was similar to that observed in the MCI group. Furthermore, this higher induction dose permitted a more rapid loss of responsiveness and was associated with a stable hemodynamic control at intubation.

In contrast with previous studies[6-9], our results showed a more rapid recovery from anesthesia by patients with the TCI system compared with the MCI system. However, it is important to point out that propofol concentrations, calculated at the effect site, were not different in the two groups at the moment of recovery from anesthesia, which is determined by the relative concentration of propofol and fentanyl at the effect site and not by the absolute concentration of propofol[10]. We also simulated the concentration of fentanyl at the effect site at the moment of recovery for each patient. Total fentanyl consumption and the calculated concentration at the effect site were not different between the groups. The difference in speed of recovery could be explained in part by the greater consumption of propofol in the MCI group, delaying the drop in the propofol levels, and not due to an effect of pharmacodynamic interaction. Also the titration of target concentrations downwards toward the end of the procedure is easier and more precise when the effect site is controlled with a TCI system, which could explain the shorter recovery times observed with the TCI system in our patients.

The ever rising pressure by health systems to reduce cost of patient care, determines the economic study of new technologies. Recently, Suttner at al[17] showed that the TCI/TIVA system is more costly compared to the more conventional anesthesia regimens. However, the TCI/TIVA system allowed a more rapid recovery from anesthesia, and was associated with a lower incidence of adverse postoperative effects and permitted earlier patient discharge from the PACU. Thus, even though the direct cost may be greater, the indirect cost is lower. These results suggest that a more extensive application of this system in medical centers, where many anesthetic procedures are administered could lead to a favorable reduction in cost.

In summary, it is concluded that both systems provided excellent clinical anesthetic conditions with a rapid and predictable recovery. However, an effect site system offer the advantages of an easier and more precise control to achieve the desired depth of anesthesia, better hemodynamic stability, and a reduction in overall propofol consumption.

REFERENCES

1. Ausems ME, Vuyk J, Hug CC Jr, Stanski DR. Comparison of a computer-assisted infusion *versus* intermittent bolus administration of alfentanyl as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 1988;68:851.
2. Alvis JM, Reves JG, Govier AV, et al. Computer assisted continuous infusions of fentanyl during cardiac anesthesia: comparison with a manual method. Anesthesiology 1985;63:41.
3. Ausems ME, Stanski DR, Hug CC. An evaluation of the accuracy of pharmacokinetic data for the computer assisted infusion of alfentanyl. Br J Anaesth 1985;57:1217.
4. Raemer DB, Buschman A, Varve JR. The retrospective use of population pharmacokinetics in a computer-driven infusion system for alfentanyl. Anesthesiology 1990;73:66.
5. Shaffer SL, Varvel JR, Aziz N, Scott JC. The pharmacokinetics of fentanyl administered by computer controlled infusion pump. Anesthesiology 1990;73:1091.
6. Russell D, Wilkes MP, Hunter SC, Glen JB, Hutton P, Kenny GNC. Manual compared with target-controlled infusion of propofol. British Journal of Anesthesia 1995;75:562-566.
7. Servin FS. TCI compared with manually controlled infusion of propofol: a multicentre study. Anesthesia 1998;53(Suppl 1):82-86.
8. White M, Kenny GNC. Intravenous propofol using a computarized infusion system. Anesthesia 1990;45:204-209.
9. Engbers HF. Target-controlled infusion in practice. European Journal of Anaesthesiology 1998;12(Suppl 10):88-90.
10. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovil JG. Propofol anesthesia and rational opiod selection. Determination of optimal EC50-EC95 propofol-opiod concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 1997;87:1549-62.
11. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controlled Clin Trials 1981;2:93-113.
12. Schuttler J, Schwilden H, Stoeckel H. Pharmacokinetic-dynamic modeling of diprivan. Anesthesiology 1986;65:A549.
13. Peacock JE, Blackburn A, Sherry KM, Reilly CS. Arterial and jugular venous bulb blood propofol concentrations during induction of anesthesia. Anest Analg 1995;80:1002-6.
14. Pagel PS, Warltier DC. Negative inotropic effects of propofol as evaluated by the regional preload recruitable strock work relationship in chronically instrumented dogs. Anesthesiology 1993;78:100-8.
15. Azari DM, Cork RC. Comparative myocardial depressive effects of propofol and thiopental. Anest Analg 1993;77:324-9.
16. Gepts E. Pharmacokinectic concepts for TCI anesthesia. Anesthesia 1998;53(Suppl):4-12.
17. Suttner S, Boldt J, Schmidt C, Piper S, Kumle B. Cost analysis of target-controlled infusion-based anesthesia compared with standard anesthesia regimens. Anesth Analg 1999;88:77-82.