TARGET-CONTROLLED INFUSION ANESTHESIA WITH PROPOFOL AND REMIFENTANIL COMPARED WITH MANUALLY CONTROLLED INFUSION ANESTHESIA IN MASTOIDECTOMY SURGERIES

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Abstract

Target-controlled infusion (TCI) system is increasingly used in anesthesia to control the concentration of selected drugs in the plasma or at the site of drug effect (effect-site). The performance of propofol TCI delivery when combined with remifentanil in patients undergoing elective surgeries has been investigated. Our aim in this study was to assess the anesthesia profile of the propofol and remifentanil target controlled infusion (TCI) anesthesia as compared to the manually controlled infusion (MCI), in mastoidectomy surgery, where a bloodless field is of utmost importance to the surgeon. Sixty patients, aged 18-60 years ASA I-II enrolled in the study, were divided into two equal groups. Group MCI received propofol and remifentanil by conventional-dose-weight infusion method, and Group TCI received propofol 4 μg/ml and remifentanil 4 ng/ml as effect-site target concentration. The hemodynamic variability, recovery profile, postoperative nausea and vomiting (PONV), surgeons satisfaction were assessed. Results were analyzed by SPSS version 11.5. The two groups were comparable with respect to age, ASA class, sex, weight, basal vital signs, operation time. The blood pressure and pulse were above desired levels in some data points in the MCI Group ($P \leq 0.05$). The PACU stay time to reach Aldret score of 10 was longer in the MCI Group (42.54 ± 8 vs 59.01 ± 6 min) ($P \leq 0.05$). The PONV was more common in the MCI Group ($P \leq 0.05$). Surgeon's satisfaction of the surgical field showed no significant differences except when described as "good", more common in the TCI Group. TCI is capable to induce and maintain anesthesia as well as MCI. In some stages of anesthesia, the TCI control of vital signs are better than the MCI. In some stages of anesthesia, the TCI control of vital signs are beter than the MCI. Recovery profile and complication rate and surgeon's satisfactions are more acceptable in the TCI than in the MCI. Group.

Keywords: Target-controlled infusion anesthesia, manually controlled infusion anesthesia, remifentanil, propofol, mastoidectomy.

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Introduction

Target controlled infusion (TCI) is increasingly used in anesthesia. This method of infusion of intravenous anesthetic drugs has been investigated for its ability to achieve targeted blood or effect site concentrations for selected drugs. Maintaining a constant plasma or effect compartment concentration of an IV anesthetic requires continuous adjustment of the infusion rate according to the pharmacokinetic properties of the drugs which can be achieved by commercially available target controlled infusion pumps. The main advantage of this infusion method among the other advantages is prompt response to signs of inappropriate anesthesia depth without any need to mathematical calculations for anesthesiologists[1].

Total intravenous anesthesia based on the administration of propofol combined with an opioid, has become a popular anesthesia technique. It allows independent modulation of the different components of anesthesia: unconsciousness, amnesia and loss of response, to noxious stimuli the first two components are controlled by hypnotics and the third by opioids. Remifentanil appears to be an ideal analgesic for total IV anesthesia (TIVA) in combination with propofol, because of its independent pathway from that of propofol as well as its rapid elimination and favorable controllability. The performance of propofol TCI delivery when combined with opioid in patients undergoing elective surgery has been investigated[2-4].

In the TCI system of delivery, the anesthesiologist, depending on the appearance of noxious stimuli, can adjust the target concentrations of propofol or remifentanil and change the infusion rate. Surgeons performing mastoidectomies as well as other otolaryngological procedures when working microscopically under high power visual field, request asanguinous surgical field. Decrease of bleeding could be accomplished by targeting higher plasma or effect site concentration of hypnotic and opioid by the TCI system. In contradistinction, the changes in infusion rates in the manually controlled infusion (MCI), could be difficult, inaccurate and time consuming.

Our aim in this study was to assess the clinical effects of propofol and remifentanil target controlled infusion (TCI) and compare them to the manually controlled infusion (MCI), in mastoid or similar surgeries.

Results

There were no statistical difference between the two groups regarding ASA class, age, sex, weight, basal vital signs and surgery duration (Table 1). Two anesthesiologists performed 60 anesthesias and 6 surgeons performed the surgery.

Table 1
Patient demographics and characteristics
(Mean and SD in parenthesis)

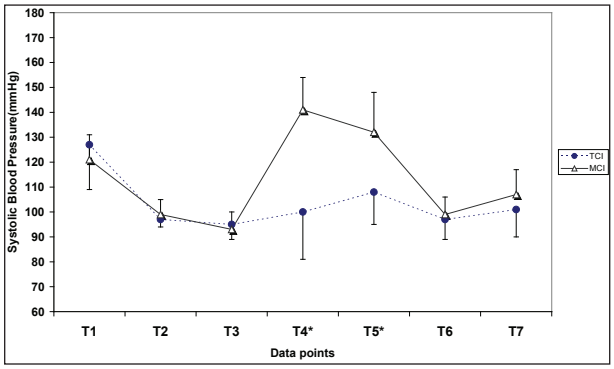
	MCI (n=30)	TCI (n=30)	* P Value
Sex (M/F)	18/12	17/13	0.55
Age (Y)	28.03 (9.79)	26.67 (8.73)	0.57
Weight (kg)	62.00 (9.70)	63.33 (12.90)	0.34
BMI (kg/m2)	23.65 (2.52)	23.50 (3.85)	0.66
BSA (m2)	1.58 (0.15)	1.65 (0.18)	0.054
ASA (I-II)	19 / 11	17 / 13	0.081
Surgery duration(min)	73.60 (17.66)	81.67 (19.63)	0.08
Baseline Systolic BP(mmHg)	125.13 (8.72)	121.27 (10.55)	0.67
Baseline Diastolic BP(mmHg)	79.37 (6.39)	79.67 (8.08)	0.69
Baseline Mean BP(mmHg)	86.60 (6.44)	84.50 (7.59)	0.98
Baseline Mean HR (Beats/min)	76.20 (8.32)	79.12 (7.61)	0.74

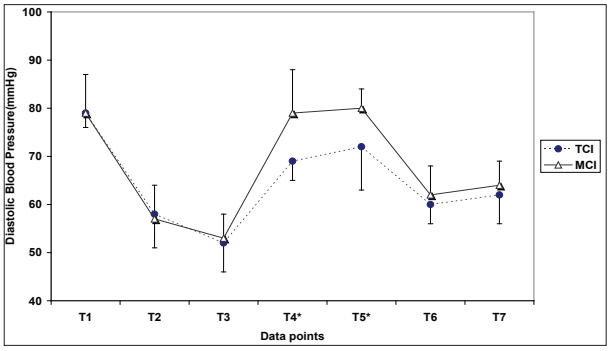
* P value < 0.05 is significant.

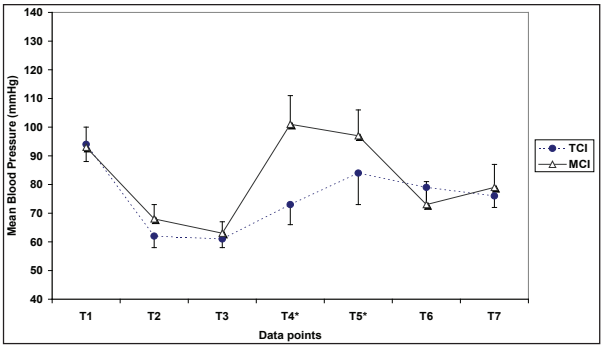
The systolic and mean arterial pressure at T4 and systolic arterial pressure at T5 data points were higher in the MCI group (P value ≤ 0.05) and no statistical differences were remarkable in the other data points (Fig. 1). There were also no statistical difference in heart rates in data points (Fig. 2).

The least BIS value recorded in data points were significantly lower in T4 and T5 data points in the MCI group (Fig. 3).

Fig. 1
Systolic, Mean and Diastolic arterial pressure in different data points in two groups (Mean±SD)







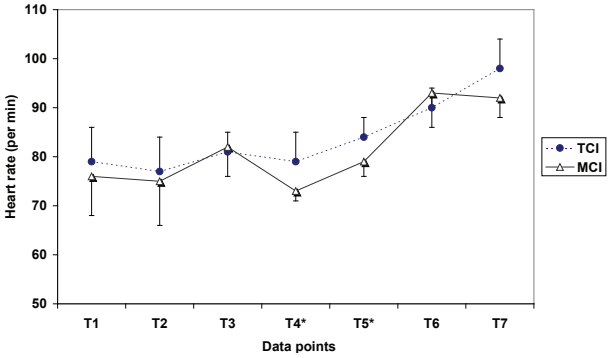
* Significant difference between two groups.

In the PACU, though there were no statistical differences between the Aldrete score between the two groups, yet the staying time for acquiring score of 10 was longer in the MCI group. The nausea and vomiting incidences were higher in the MCI group and same symptoms continued higher in the surgical ward (Table 2).

The total consumption and rate of consumption of Remifentanil and propofol were significantly higher in the MCI when compared to the TCI group (Table 3).

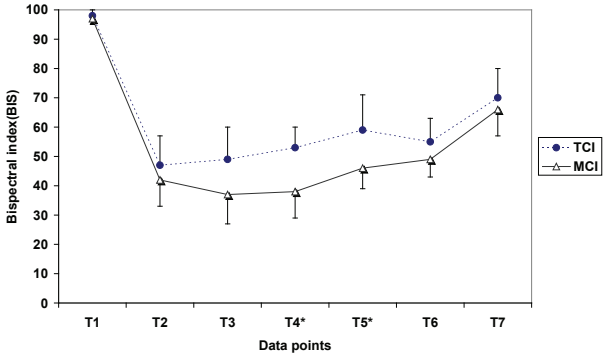
There were no differences in the time from the end of administration of anesthetics to eye opening

Fig. 2
Heart rate during different data points in two groups (Mean ± SD)



*Significant difference between two groups

Fig. 3
BIS changes during different data points in two groups (Mean±SD).



*Significant difference between two groups

Table 2
Duration of post anesthesia care unit (PACU) residence, incidence of postoperative side effects and recovery characteristics (Mean and standard deviation in parenthesis).

	TCI (n=30)	MCI (n=30)	* P value
PACU			
Length of stay (min)	42.54 (8)	59.01 (6)	0.00
Aldrete Scoring receiving PACU	7.2 (1.0)	6.4 (0.4)	0.06
Nausea (n of patients)	6 (18%)	14 (42%)	0.00
Vomiting (n of patients)	3 (9%)	11 (33%)	0.00
Shivering (n of patients)	9 (27%)	10 (30%)	0.40
Ward			
Nausea (n of Patients)	10 (30%)	17 (51%)	0.01
Vomiting (n of patients)	2 (6%)	6 (18%)	0.00
Shivering (n of patients)	0	1 (3%)	0.50
*P value < 0.05 is significant			

Table 3
Propofol and remifentanil consumed in two groups (Mean and standard deviations in parenthesis)

	MCI	TCI	* P Value
Total Propofol administered (mg)	1178.83 (187.86)	872.73 (274.05)	0.000
Propofol used per weight and time (μg/kg /min)	138.81 (20.17)	107.84 (25.09)	0.007
Total remifentanil administered (mg)	1324.23 (189.18)	955.07 (285.14)	0.005
Remifentanil used per weight and time (μg/kg /min)	0.33 (0.04)	0.19 (0.04)	0.001

* P value < 0.05 is significant.

Table 4
Prediction of awakening time by pump, eye opening time, obey to commands time (extubation time) , time to reach Aldrete score 10 and drug costs in two groups (Mean and standard deviation in parenthesis).

	MCI	TCI	*P Value
Prediction of awakening (min)	8.83 (2.53)	8.33 (2.92)	0.43
Eye opening time (min)	9.00 (2.24)	8.76 (2.81)	0.72
Obey to commands time (min)	9.26 (2.19)	9.11 (2.89)	0.82
Time to reach Aldrete score 10	59.01 (6.77)	42.54 (8.32)	0.00
Total cost of drugs ($)	35.35 (6.53)	29.09 (7.80)	0.00
Cost per minute ($)	0.57 (0.10)	0.45 (0.08)	0.00

* P value < 0.05 is significant.

(awakening time) and to extubation time (obey to commands time) in the two groups (Table 4).

The costs of anesthetic drugs (propofol and remifentanil) and cost of one minute of anesthesia, was higher in the MCI than in the TCI group (0.57 ± 0.10 dollar vs 0.45 ± 0.08 dollar) (Table 4).

Materials and Methods

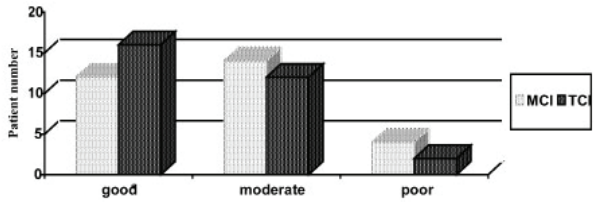
Following approval of the Ethics Committee of our institution and patient written informed consent, 60 patients 18-60 years. ASA I-II scheduled for mastoidectomy with a planned duration of what than 30 minutes, were included in the study. Exclusion criteria consisted of patients under 18 and above 60 years, ASA physical status more than II, hypertriglyceridemia, alcohol or opium dependence or drug abuse and use of beta adrenergic receptor blocking agents or α2 adrenergic receptor agonists.

All patients were unpremedicated. Patients were randomly allocated into two groups (30 each) by sealed envelop technique; group target controlled infusion group (TCI) and group B or manually controlled infusion group (MCI). On arrival to the OR the weight of patients were measured by electronic weighing-machine and then, electrocardiogram leads, pulse oximetry and noninvasive blood pressure, were attached. A 20 gauge IV cannula was inserted in antecubital vein in all patients. Ringer solution 10 cc/kg of body weight was infused intravenously before induction of anesthesia. Bi-refferential electroencephalogram (EEG) leads (Aspect medical system BIS-XP version 3.23, USA) were attached after skin preparation and disinfection with alcohol and slight rubbing. When electrode impedance exceeded 10 KΩ, the electrode was replaced and skin preparation was repeated.

In (TCI) group anesthesia was induced with propofol 1% (Braun Melsungen, Germany) and remifentanil 50 μg/ml (GSK, UK) simultaneously administered by two separate modules of a continuous computer assisted TCI system (Fresenius Kabi Company, Base Prima and DPS Module System, France). Before induction of anesthesia, patients' weight and height, age, sex and target of effect site concentration of propofol and remifentanil were entered into the TCI system. The initial effect site target of propofol was set at 4 μg/ml, titrated against clinical effect and BIS values, and the initial effect site target of remifentanil was 4 ng/ml, titrated against vital signs. We used Schnider and Minto three compartments pharmacokinetic models for propofol and remifentanil respectively (5-6). The goal of propofol administration was to maintain BIS level from 45 to 60.

After hypnosis (lack of eyelid reflex), atracurium (0.5 mg/kg) was administered IV slowly to achieve muscle relaxation for endotracheal intubation. The atracurium dose was repeated to maintain post tetanic count zero. After intubation the effect site concentration of propofol and remifentanil were adjusted to maintain the BIS level from 45 to 60 and 55 < MAP > 85 mmHg. BIS values beyond the desired levels were managed with increasing or decreasing 1 μg/ml from propofol effect site target concentration, and MAP far from desired levels also managed with increasing or

Fig. 4
Satisfaction of surgeons about surgical field.



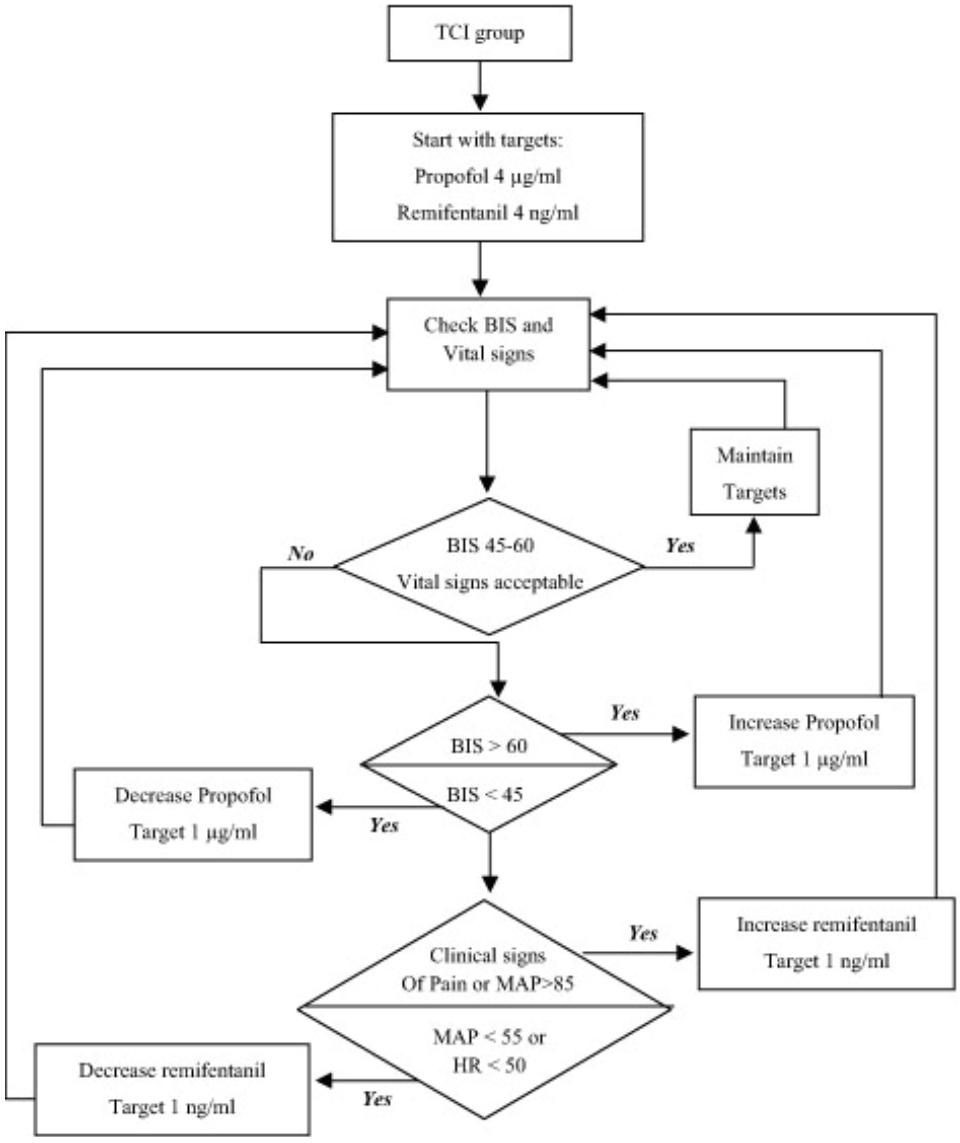
* In good condition difference between two groups is significant.

decreasing 0.5 ng/ml to effect site target concentration of remifentanil (Flowchart1).

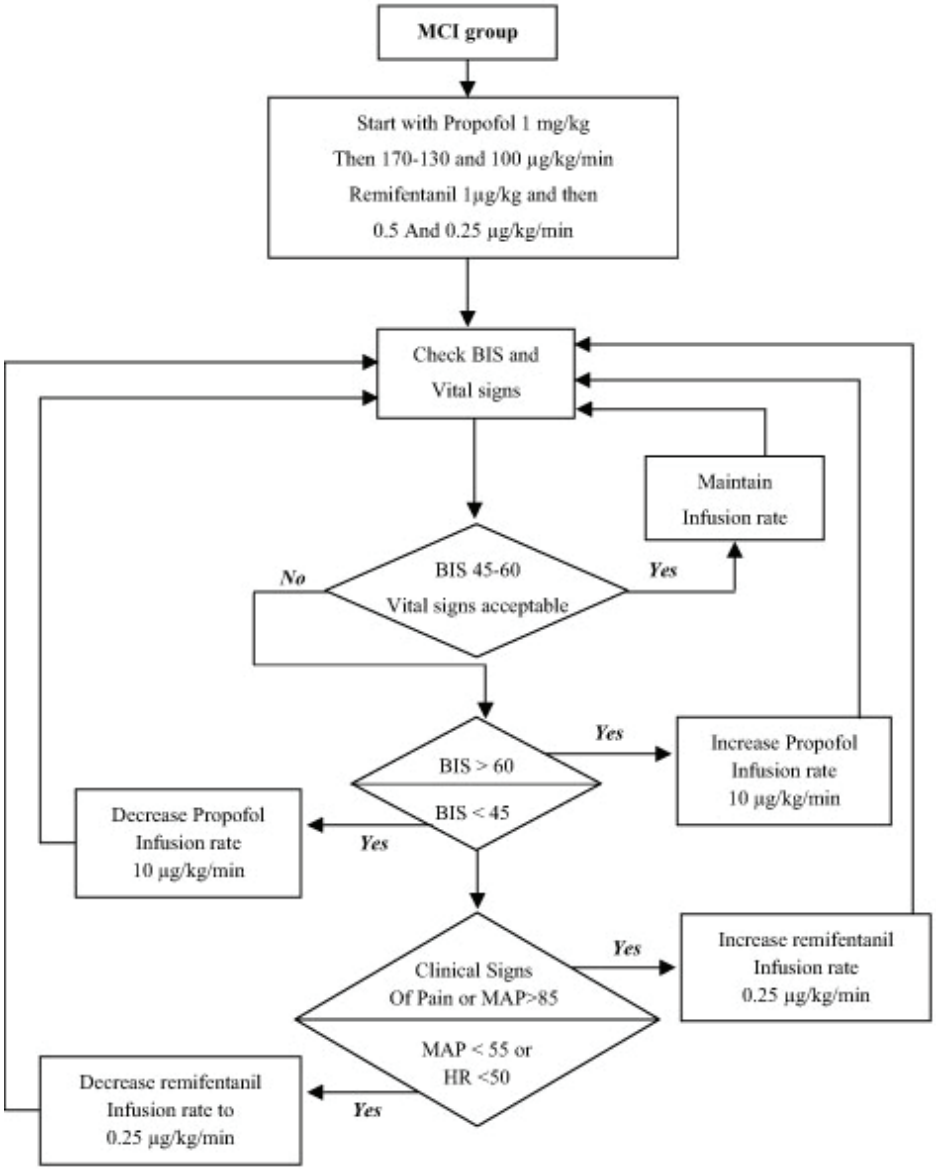
With decreasing of MAP < 55 mmHg, crystalloids (Ringer solution) were infused and until a clinically adequate volume load was achieved a vasopressor (Ephedrine) 2.5 mg i.v was administered to restore MAP immediately. With increasing MAP > 85 mmHg increasing the effect site concentration of remifentanil was repeated step by step until reaching remifentanil target to 10 ng/ml and if this failed to reduce MAP < 85 mmHg, infusion of trinitroglycerine 5 μg/min was added.

In the MCI group anesthesia was induced with bolus propofol infusion 1 mg/kg and after that 170 μg/kg/min for 10 minutes, and then 130 μg/kg/min for 10 minutes and finally 100 μg/kg/min for maintenance of anesthesia. This method of propofol infusion produces and maintains propofol plasmatic concentration about 4 μg/ml[7]. Remifentanil infusion was started with

Flowchart 1
Anesthetics administration algorithm in TCI group



Flowchart 2
Anesthetics administration algorithm in MCI group



slow bolus dose of 1 µg/kg and then was continued 0.5 µg/kg/min. After loss of consciousness atracurium was administered, repeated and managed as the same manner as in TCI group. The goals of anesthesia were the same as in TCI group. BIS values and MAP out of the desired range was managed with increasing or decreasing of propofol and remifentanil infusion rate 10 µg/kg/min and 0.25 µg/kg/min respectively (Flowchart 2).

In both groups patients were ventilated to maintain normocapnia ($ETCO_2$ between 36-44 mmHg with mixture of oxygen in air (FIO_2 40%). In all patients the continuous infusion of propofol and remifentanil were stopped at the beginning of skin closure when 2 mg morphine sulphate and 4 mg ondansetrone were administered intravenously for postoperative analgesia and prophylaxia of nausea and vomiting.

The time from stopping the infusion until patients opened their eyes (eye opening time), obeyed to commands and underwent tracheal extubation (extubation time) and the time from stopping the infusion until Aldrete score of 10 were documented and compared in two the groups[8]. Six different surgeons blinded to anesthesia method conducted were asked

about their satisfaction about asanguineous surgical field which was described as good (without disturbing bleeding), moderate (minimal bleeding not disturbing surgery) and poor (bleeding disturbing surgery).

Seven data points were defined for monitoring and documentation of vital signs and BIS: T1, before the induction of anesthesia; T2, before intubation; T3, three minutes after tracheal intubation; T4, three minutes after skin incision; T5, during mastoidectomy; T6, during tympanic membrane placement and T7, before skin closure.

The costs of intravenous anesthetic drugs (disposables, nursing, staff, oxygen, air, vasopressors and antiemetics were not included) were taken from hospital pharmacy list.

Data were presented as mean with standard deviation in parenthesis unless otherwise stated. For statistical analysis SPSS software (version 11.5) was used. Hemodynamic variables were analyzed with two factorial analysis of variance for repeated measurements. Student's t-test was applied at the end point of each measurement. In case of multiple comparisons, P values were corrected according to Bonferroni. Fisher's exact tests, X^2 tests, leven tests, Mann-Whitney U-tests, or nonpaired student's t-tests were used when appropriate. P values < 0.05 were considered significant.

Discussion

In this study we used propofol as hypnotic together with remifentanil as analgesic for induction and maintenance of anesthesia. Propofol is presently the most common intravenous anesthetic used for total intravenous anesthesia. Pharmacokinetic model-driven infusion of propofol has become widely available worldwide. In addition, remifentanil is the newest μ-agonist available for administration as an analgesic during surgery and it is best administered as an infusion because of its metabolism by general body esterases.

Interaction of these two drugs in preventing responses to noxious stimulation is investigated. Increasing the duration of the infusion has minimal impact on recovery time if the optimal dose of remifentanil is not used[9]. Hence combination of these two drugs has become more popular for intravenous anesthesia. Regardless of the kind of surgery, remifentanil improves intraoperative hemodynamic stability when compared to other opioids: Twersky reported better hemodynamic control when remifentanil used compared with fentanyl[10] and Mackey confirmed better control of tachycardia and hypertension in very high risk outpatients laryngoscopies with remifentanil as compared to fentanyl[11]. In our study remifentanil was used as an analgesic in both TCI and MCI, however, the TCI group when surgical stimuli were profound showed more stable hemodynamic parameters in different data points at T4 (three minutes after skin incision) and T5 (during mastoidectomy). This is very important in mastoidectomy operations because bleeding in surgical field is directly related to blood pressure and even when minimal bleeding may disturb the ideal condition for surgery.

Remifentanil is associated with faster recovery and extubation time because of its rapid hydrolysis and decreased hypnotic requirements. This can affect early and late recovery and discharge time of patients from operating table to the (PACU) and eventually to surgical wards and finally to home. Remifentanil as an anesthetic used as TCI method has showed superiority to the conventional manually controlled infusion (MCI).

Various studies have shown that hemodynamic stability, recovery time, and discharge time have improved by the use of TCI for the administration of remifentanil and propofol in the induction and maintenance of anesthesia[12-13]. Despite these findings other authors could not show significant hemodynamic differences between TCI and MCI group during induction and maintenance of anesthesia[14-15].

We think the findings in our study are the result of administration both hypnotic and analgesic with TCI technique which allows fine titration of effect-site target concentration counter effecting the noxious stimuli. The TCI enables anesthesiologist to rapidly change the effect-site target concentration of desired drug for desired response without need to time-occupying mathematical calculation to adjust infusion rate for body mass of the patient. Also our findings demonstrated the efficacy of TCI in controlling anesthesia depth during different stages of surgery as well as MCI. Although all patients were received

to PACU with comparable Aldrete score, the MCI patients, however, stayed more in this unit to reach Aldrete score 10. In other word, intermediate recovery time (discharge from PACU to surgical ward) was longer in the MCI group. This correlates with total propofol and remifentanil consumed during anesthesia observed more in the MCI group.

Although we found less drug consummation and decreased drug cost in the TCI group, literature review is contradictory, Suttner found that TCI using propofol and remifentanil was the most expensive anesthesia regimen, with total intraoperative costs almost two fold compared with the standard IV propofol regimen and almost four times larger compared with a standard inhaled anesthetic with isoflurane in sixty patients undergoing elective laparoscopic cholecystectomies[12]. Fombeur and coworkers described a standard regimen of desflurane was more cost-effective than TCI propofol for anesthesia maintenance in achieving post operative nausea and vomiting free episodes in otlogical surgeries[16] Russell and coworkers[17] found significantly more propofol was administered during both induction and maintenance of anesthesia with the target controlled system while no clinically significant difference in heart rate and hemodynamic variables were observed. On the other hand De castro and coworkers reported significantly smaller requirements of remifentanil without a difference in propofol requirement and at the same time more common intraoperative hypotension episodes in MCI group patients than TCI group[18].

Limitation of our study lies in the fact that our data collection was not performed continuously in all times of the operation but in selected data points in which hemodynamic imbalance episodes were more probable. Despite this limitation data in the postoperative time were collected continuously in which the PONV and the shorter staying time in recovery room to reach Aldrete score of 10 the TCI group.

The possible explanations can explain the contradictory results with the tel system, consiste that studies used only hypnotic or analgesic and in others both been administered by TCI. Fine titration of hypnotic and/or analgesic target concentration against clinical effects can rapidly produce desired clinical situation without time delay and uncontrolled hemodynamic changes. Changing effect-site target concentration of every drug and attention to drug pharmacodynamic instead of drug pharmacokinetic can result to more stable hemodynamic variables, less drug consumption and shorter recovery time[19]. On the other hand biovariabilty plays an important role in different responses to identical target concentration in various studies[20]. Several models have been proposed and validated for their ability to predict drug concentration in the plasma or effect site compartment for propofol and remifentanil. Biovariability and severeal pharmacokinetic models produces different results when TCI is used. In summary remifentanil-propofol TCI-based anesthesia achieved better hemodynamic stability through the stages, better recovery profile, decreases drug costs of anesthetics and more satisfaction of surgeons about surgical field condition, as compared to the manually controlled infusion (MCI) anesthesia, in mastoidectomy surgeries.

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