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*Original Article*

# A bispectral index guided comparison of target-controlled versus manually-controlled infusion of propofol and remifentanil for attenuation of pressor response to laryngoscopy and tracheal intubation in non cardiac surgery

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## Abstract

**BACKGROUND:** Target-controlled infusion is a new delivery system for intravenous anesthetic agents with which the anesthetist targets a plasma or effect-site drug concentration to achieve a predetermined effect. With this system, the tedious task of calculating the amount of administered drug required to achieve the target concentration is left in charge of a microprocessor which commands the infusion device. In this prospective study we compared alterations in blood pressure and heart rate from initiation of induction of anesthesia until 3 minutes after tracheal intubation in two methods of drug infusion, target-controlled infusion (TCI) and manually controlled infusion (MCI). Total anesthetic drug used until 3 minutes after intubation and level of produced hypnosis also were compared between two methods.

**METHODS:** 40 patients were enrolled in this clinical trial study and were allocated randomly in two groups, each group consisting of 20 patients. In TCI group, patients received propofol and remifentanil with TCI pump to achieve 7 µg/ml and 4 ng/ml as plasmatic target drug levels, respectively. In MCI group, patients received propofol 2 mg/kg and remifentanil 1 µg/kg of body weight with manually controlled infusion. Both groups received succinylcholine as muscle relaxant to facilitate laryngoscopy and tracheal intubation. Bispectral index (BIS) was passively recorded in two groups to compare the level of hypnosis. Blood pressure (BP) and heart rate (HR) were recorded at 5 different times (T-1, T0, T1, T2 and T3). Independent t-test and paired t-test were used for data analysis.

**RESULTS:** Systolic arterial pressure (SAP) was not different at T-1 between two groups but systolic hypotension was seen in MCI group more than TCI group at T0 ($P<0.05$). Systolic hypertension was more common in MCI group after intubation; i.e. SAP showed significant differences in T1, T2 and T3 between two groups ($P<0.05$). Mean arterial pressure (MAP) showed significant difference only at T0 and T1 between two groups. Also, heart rate in MCI group was higher than that in TCI group at T1 and T2. Mean used propofol was 128.10 ± 11.30 mg in MCI group versus 140.90 ± 16.21 mg in TCI group ($P<0.05$) and the least BIS value recorded was 31.4 ± 10 in MCI group versus 42.5 ± 12.3 in TCI group ($P<0.05$).

**CONCLUSIONS:** Hypotension in MCI group was seen more frequently than that in TCI group after induction and before laryngoscopy (T0). Hypertension and tachycardia were seen in MCI group more commonly than those in TCI group after laryngoscopy and tracheal intubation. Then, we recommend TCI technique in high risk patients for attenuation of the pressor response to laryngoscopy and tracheal intubation. Also, we recommend further researches in other educational centers to compare the effect-site TCI with plasmatic TCI in controlling pressor response.

**KEY WORDS:** Anesthetic techniques, intravenous infusion, target-controlled infusion, propofol, remifentanil, bispectral index.

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Laryngoscopy and tracheal intubation cause a marked pressor response, raising the arterial pressure and heart rate significantly [1]. Arrhythmia, increased plasma catecholamine concentrations and myocardial ischemia are other adverse effects of this pressor response which may be potentially harmful in patients with cardiac disease, raised intracranial pressure and hypertensions [2,3].

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Preserving blood pressure and heart rate in a narrow range is always a concern of anesthesiologists before inducing anesthesia, especially if the patient has limited cardiovascular reserve or any intracranial pathology. New drugs and infusion techniques can induce anesthesia more purposefully with lower cardiovascular events compared with traditional techniques. Target-controlled infusion (TCI) system is a new anesthetic drug delivery device, which maintains a desired "target" concentration of drug in plasma or effect site (biophase) [4,5]. Reaching a desired plasmatic drug concentration means desired clinical drug effect without time-consuming mathematical calculation for physician. In this technique, anesthetic drug infusion rate is set pharmacokinetically based on weight, age, height and sex of patient and finally target plasma drug concentration will be determined by the anesthesiologist. Although improved cardiovascular and respiratory stability during maintenance of anesthesia is found in some studies in TCI based anesthesia, yet none of them investigated the effects of TCI on laryngoscopy and tracheal intubation hemodynamic status [6,7]. The aim of this study was to compare the alterations of blood pressure (BP) and heart rate (HR) before laryngoscopy and intubation and after laryngoscopy and intubation in patients with target-controlled infusion of propofol and remifentanil and manually controlled infusion of these drugs to attenuate the pressor response of laryngoscopy and tracheal intubation. Also, we compared the level of propofol induced hypnosis in patients with guidance of BIS.

## Methods

After obtaining the approval of our institutional ethics committee and written informed consent, 40 ASA (American Society of Anesthesiologists) physical status I-II patients, aged 20-60 years, who were scheduled for elective surgeries requiring orotracheal intubation in Imam Khomeini Hospital of Kermanshah University of Medical Sciences and Health Services in Kermanshah, Iran in 2005 were prospectively enrolled.

Exclusion criteria were any treated or untreated hypertensive disease, history of any sensitivity or contraindication of using propofol, using beta and calcium channel blockers, angiotensin converting enzyme inhibitors, vasodilators or $\alpha_2$-agonist agents, and chronic use of any sedative or opioid derivatives. Also, any predicted difficult intubation was excluded from the study.

Patients were unpremedicated and before induction, a cannula was inserted into a large forearm vein in the waiting room; basal vital signs were measured and ringer's solution 10 ml/kg was infused. We monitored 3 leads electrocardiogram (I, II, and III leads), noninvasive blood pressure, heart rate, pulse oximetry, and temperature (Datascope monitoring system model passport II, manufactured in USA) when the patients lied on operating table. BIS was measured by BIS monitor and sensor (Aspect medical system, MA; BIS Host Rev 3.23, USA). BIS was measured at the frontal lobe of the dominant hemisphere after skin preparation with alcohol and slight rubbing by skin soap. BIS measurement was begun before anesthesia induction and was recorded every 30 seconds during induction. We also used the TCI pump (Fresenius Kabi Company, Base Prima and DPS module system, France) for both target-controlled and manually-controlled infusion of drugs. Patients were allocated randomly (by sealed envelope system) into two groups according to drug administration technique. In MCI group, patients received remifentanil (Glaxosmith pharmaceutical, UK) 1 $\mu$g/kg in 60 seconds and propofol 2 mg/kg as propofol lipuro 1% (Braun pharmaceutical, Melsungen, Germany) in 2 minutes. Both drugs were administered with DPS module as weight adjusted, manually-controlled infusion. When BIS value decreased to 60, succinylcholine 1.5 mg/kg was administered and after 90 seconds ventilating with mask and pure oxygen, laryngoscopy and tracheal intubation were done. In TCI group patients received propofol and remifentanil with TCI method to

achieve 7 $\mu$ g/ml and 4 ng/ml as plasmatic target concentrations, respectively. Propofol concentration was 10 mg/ml and Schnider protocol was chosen as pharmacokinetic model. Remifentanil concentration was 50 $\mu$ g/ml and Minto protocol was chosen as pharmacokinetic model. Both drugs were administered in a way that induction time achieved over 2 minutes. With decreasing BIS value to 60 and reaching the desired (target) plasmatic drug concentration, succinylcholine 1.5 mg/kg was administered and after 90 seconds ventilation with mask and pure oxygen, trachea was intubated. An invariable experienced anesthesiologist intubated all patients` tracheae. Any prolonged laryngoscopy more than 15 seconds or trying laryngoscopy more than one time was excluded from the study. HR and BP were recorded with automated non-invasive HR and BP monitoring at five different times as below: before any drug administration (T-1), before laryngoscopy (T0), and 1, 2 and 3 minutes after tracheal intubation (T1, T2, and T3). Mean administered propofol and remifentanil until the end of intubation were recorded and then, maintenance of anesthesia was continued with TCI total intravenous anesthesia in all patients.

The estimated sample size was 19 patients per group to detect with a power of 90% and an = 0.05, a difference of at least 15% in BP relating to baseline BP which was defined as clinically relevant. Independent t-test was used to compare quantitative variables between two groups and paired t-test was used to compare quantitative variables within each group. The statistical analysis included data of all patients according to intension to treat analysis. Results are expressed as mean ± standard deviation unless otherwise stated. A value of $P<0.05$ was considered significant. The data were analyzed using SPSS software version 12.

**Results**

Demographic data showed no significant differences between two groups (table 1). No patient was withdrawn from the study because of an adverse event or impossible operating condition. Although systolic arterial pressure (SAP) was not different before induction (T-1) between two groups but was significantly different after induction and before laryngoscopy (T0) between two groups. Differences were also significant in 1, 2 and 3 minutes after laryngoscopy compared with basal SAP (T-1) within MCI group (figure 1). No significant difference of SAP was found within TCI group between different data points. Mean arterial pressure (MAP) showed significant difference in T0 between two groups. Decreased MAP was obvious in MCI group compared to TCI group. MAP in MCI group also showed significant decrease in T0 compared to T-1 and significant increase in T1 compared to T-1. In TCI group no significant differences of MAP were seen in different data points (figure 2). Diastolic arterial pressure showed no significant difference before and after anesthesia and laryngoscopy both between two groups and different data points within the same group.

HR showed significant increase in T1 and T2 compared with T0 in MCI group; i.e. tachycardia was more common in T1 and T2 compared to baseline. HR also showed significant increase in T1 and T2 in MCI group compared with T1 and T2 in TCI group, respectively which notes more common tachycardia in MCI group compared to TCI group after tracheal intubation. In TCI group, HR showed no significant differences in different data points (figure 3).

Total used propofol until intubation of trachea was 128.10 ± 11.3 mg in MCI group versus 140.9 ± 16.21 mg in TCI group which showed significant difference. Also, mean used remifentanil showed no difference between two groups with 63.2 ± 3.4 μg in MCI group versus 68.7 ± 4.81 μg in TCI group. Although bispectral index was recorded passively and not used for titration of drugs, results showed deeper level of hypnosis in classic manually controlled group (MCI group). The least recorded BIS value was 31.4 ± 10 in MCI group and 42.5 ± 12.3 in TCI group which showed significant difference.

**Table 1**. Patients' demographic data.

| | MCI (n = 20) | TCI (n = 20) |
|---|---|---|
| Age (yr) | 37.4 ± 4.9 | 39.0 ± 3.7 |
| Gender (M/F) | 12/8 | 13/7 |
| Physical Status I/II (ASA) | 17/3 | 16/4 |
| Body Weight (kg) | 61.8 ± 7.2 | 59.9 ± 6.4 |
| Height (m) | 1.59 ± 0.08 | 1.61 ± 0.07 |
| Body Surface Area ($m^2$) | 1.71 ± 0.23 | 1.72 ± 0.64 |
| Body Mass Index ($kg/m^2$) | 23.6 ± 2.24 | 22.3 ± 3.84 |

No significant differences were seen between two groups (P>0.05)

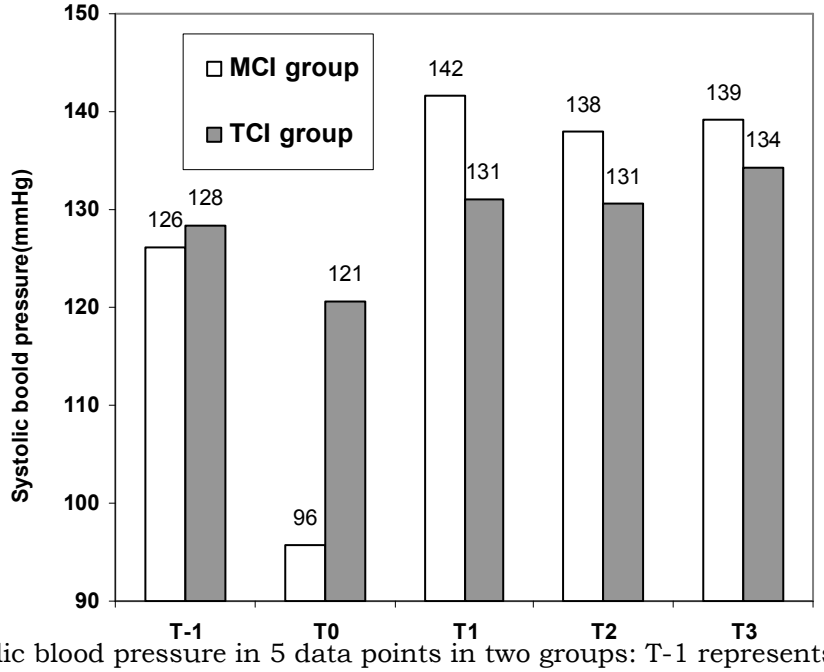


**Figure 1.** Systolic blood pressure in 5 data points in two groups: T-1 represents base line point, T0 represents the point after induction and before laryngoscopy, and T1, T2 and T3 represent 1, 2 and 3 minutes after intubation, respectively**.** Values at T0 showed significant differences with T-1 values in the same group (P<0.05)**.** Values at T1 showed significant differences with the same data point values in other group (P<0.05).

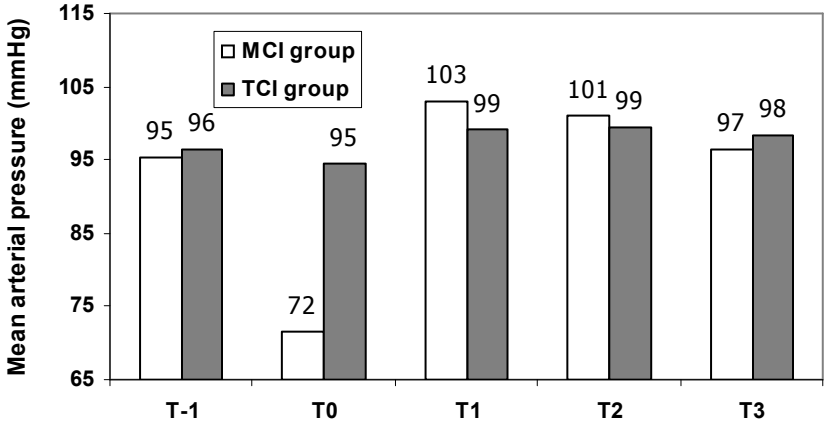


**Figure 2.** Mean arterial pressure in 5 data points in two groups.
Values at T0 showed significant difference with baseline values (T-1) and with values at T0 in another group. Values at T1 showed significant difference with values at T0 in the same group (P<0.05).

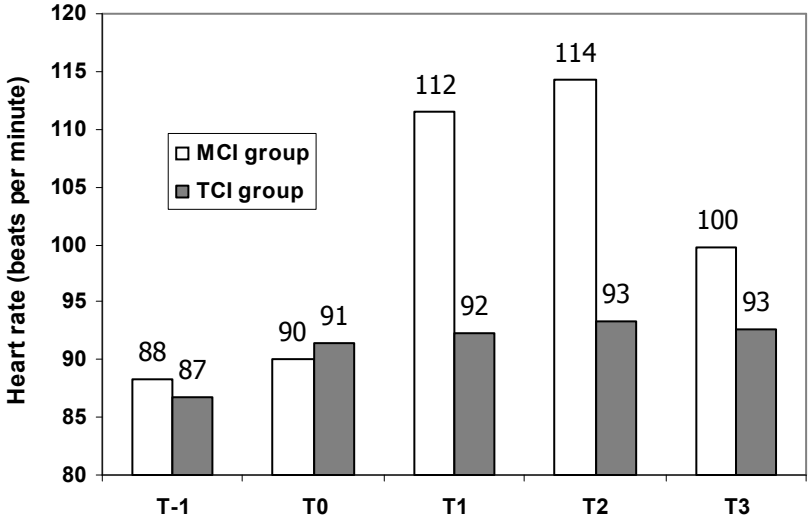


**Figure 3.** Mean Heart rate in 5 data points in two groups.
Values in T1 showed significant differences with those in other groups at the same data point.
Values at T2 showed significant differences with values at T0 in the same group (P<0.05).

## Discussion

According to the results we found more stable hemodynamic parameters with TCI technique after laryngoscopy and tracheal intubation in spite of more propofol administered in this group. Breslin and colleagues found the total dose of propofol used was higher in the target controlled group (9.9 ± 1.6 mg/kg/h) compared with the manually adjusted group (8.1 ± 1 mg/kg/h, P<0.05) [8]. This was true for the whole duration of anesthesia and not for induction period only. But, as the difference in the total used propofol is mainly due to higher rate of propofol administration in the first 30 minutes of anesthesia in the TCI method, [9,10] we can generalize this to our TCI group patients too.

BIS value was passively recorded in this study and was not used for titration of drug infusion. In MCI group, BIS values showed deeper hypnosis. This is probably due to the entrance of drug mass to circulation and excess plasmatic drug levels. But, in TCI group as the hypnotic drug was titrated smoothly and step by step by TCI pump no peak plasmatic drug level was produced; hence, higher BIS values were recorded in this group of patients in spite of more hypnotic drug used; i.e. the drug was administered more purposefully. In contrast, Breslin and colleagues found lower BIS scores in the target controlled group, which was significant over the first 15 minutes of anesthesia [8]. This difference could be due to factors such as anesthesia being administered by anesthetists more experienced with TCI technique, anesthesia being carefully titrated to the clinical endpoint (like closed loop TCI instead of model based TCI), use of some adjuvants such as nitrous oxide and finally, use of different analgesics other than remifentanil like fentanyl and sufentanil with varying doses which have widespread and potent effects on propofol for producing levels of hypnosis due to synergism [11-13]. Also, in this study we set the plasmatic remifentanil concentration conservatively at 4 ng/ml, while therapeutic window of remifentanil is broad and this drug has potent synergistic effects in reducing propofol dose and producing lower BIS values at the same plasmatic propofol concentration [13-15]. On the other hand, we didn't use any premedication (analgesic or anxiolytic) in patients which could deviate the pharmacokinetic parameters and produce deeper hypnosis and lower BIS values with lower plasmatic drug concentrations [9,16].

Alvis and colleagues showed that infusion of fentanyl during cardiac anesthesia in a method named CACI (computer assisted continuous infusion) which is synonymous with TCI, produces greater hemodynamic stability and fewer adjuvants drug interventions and significantly fewer hypotensive and hypertensive episodes compared with the manual infusion group [17]. They didn't note which kind of open or closed cardiac surgeries were done in patients but, demonstrated that significantly more fentanyl received in the stable fentanyl blood level group. Also, Hentgen and colleagues found that the TCI based anesthesia with sufentanil and propofol conducts anesthesia with more hemodynamic and electroencephalogram stability compared with manually controlled anesthesia in thyroid surgery [18]. These findings are resembled to our findings for the most noxious stimulation in surgery, laryngoscopy and tracheal intubation.

Finally, as mentioned earlier, few researchers have studied the clinical profile of target-controlled infusion but, we were not able to find any literature about advantages of TCI to manually controlled method in attenuating pressor response of laryngoscopy and tracheal intubation. Also, we recommend TCI based anesthesia in high risk patients for pressor responses such as ischemic heart disease, hypertension, hyperthyroidism, pheochromocytoma, and increased intracranial pressure. The second recommendation is doing further researches in other educational centers and comparing the effect-site TCI with plasmatic TCI in attenuating pressor responses. Although this device is expensive and not available in all operating theatres but, as this method of drug administration provides control of hemodynamic variable better than that in classic weight adjusted manually controlled infusion anesthesia and doesn't need any time-consuming mathematical calculations for anesthesiologist, anesthetists must practice and get experience in this method.

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