Original Article

Comparison of recovery profiles in target-controlled infusions (TCI) versus manually controlled infusions for total intravenous anesthesia (TIVA) in laparoscopic surgeries. A randomized controlled trial

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Abstract

Background and Aims: Considerable importance has been attached to early recovery and discharge readiness after surgeries. Many centers use total intravenous anesthesia (TIVA) as their anesthesia technique of choice. Target-controlled infusions (TCI) have been proposed as a method to precisely deliver continuous infusions of propofol and opioids as compared to the traditionally used manual-controlled infusion (MCI) methods. However, TCI has also been shown to result in the administration of larger doses of propofol which could cause delayed emergence and recovery from anesthesia. Studies involving TCI have focused mainly on its effects on anesthesia induction but not much literature is available on recovery profiles of patients on TCI. This study was designed to compare the effect of conventionally used MCI methods versus the target-controlled infusion (TCI) method of administering TIVA on recovery characteristics in patients undergoing laparoscopic surgery.

Material and Methods: This was a prospective randomized interventional study on 54 patients. Our primary objective was to compare the rates of recovery from anesthesia as judged by four parameters. Time to return of spontaneous ventilation, time to respond to verbal commands, time to extubation, and time to shift patient out of the operating room after stoppage of propofol infusion. As secondary objectives, intraoperative average bispectral index (BIS) values and total anesthetic drugs (propofol and fentanyl) consumption were also compared.

Results: We noted that for laparoscopic surgeries lasting less than 4 hours, both MCI and TCI techniques of TIVA have comparable rates of recovery after the stoppage of propofol infusion. Total consumption of propofol and fentanyl was also similar; however, with the use of the TCI method of TIVA, better depth of anesthesia as evidenced by lower average BIS levels was noted.

Conclusion: Recovery rates after TIVA using a target-controlled infusion (TCI) system are similar to BIS-guided MCIs in patients undergoing laparoscopic surgery lasting less than 4 hours. TCI resulted in better depths of anesthesia though per kg/min consumption of propofol was found to be more.

Keywords: Intravenous anesthesia, laparoscopy, propofol, patient discharge

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Introduction

Considerable importance has been attached to early recovery and discharge readiness after surgeries these days. Optimizing operating room (OR) utilization especially after daycare surgeries has significant cost implications for the hospital. Many centers are now using total intravenous anesthesia (TIVA) as the anesthesia technique of choice. Several anesthetic agents have been incriminated in burning a hole in the ozone layer leading to global warming.[1] Thus, there has been a conscious shift toward TIVA to maintain a green and clean environment.

TIVA is usually practiced by manually controlling infusion rates to maintain a stable hemodynamic and a bispectral index (BIS) value between 40 and 60. With target-controlled infusion (TCI), target blood or effect-site concentration can be set. Manual infusion systems consider only the actual weight of the patient whereas TCI pumps incorporate algorithms that require the patient's age, gender, weight, and height to calculate the rate of drug administration for achieving desired plasma levels or effect-site concentrations precisely. Conventional infusion systems cannot increase or decrease drug concentrations rapidly enough to account for abrupt increases or decreases in stimulation. Conventional infusion systems cannot even maintain steady drug concentrations in the plasma or brain during periods of constant stimulation. All these factors are taken into consideration in TCI systems.

Randomized trials have explored the differences in quality of anesthesia, adverse event rates, and cost between TCI and manual-controlled infusion (MCI) but the effectiveness of TCI compared with MCI remains controversial especially for recovery profile assessments.[2]

TCI systems have been shown to result in the administration of larger doses of propofol.[3] This may result in delayed emergence and recovery from anesthesia. The ability to predict individual propofol effect-site concentration (Ce) for return of consciousness (ROC) would allow the dose of propofol to be adjusted to achieve an adequate ROC. By knowing the associated factors that predict Ce-ROC, the anesthesiologist should be able to estimate the emergence time and provide a fast emergence to shorten the anesthesia-controlled time.[4]

This study has been designed to compare the effect of MCI versus TCI of propofol on recovery characteristics in patients undergoing laparoscopic surgery under TIVA. As a secondary objective, we also measured the total consumption of propofol while using the two methods.

Material and Methods

After taking Ethical committee approval, a prospective randomized trial was registered prospectively vide CTRI number: CTRI/2018/06/014366. All patients in the age group of 18–70 years, belonging to American Society of Anesthesiologists' (ASA) Grade of I–III undergoing laparoscopic surgery presenting to our tertiary cancer care hospital were included. Patients with contraindication to propofol use, any known cardiac illness, or with body mass index (BMI) >30 kg/m^2 were excluded from the study. After taking written informed consent, all included patients were randomized based upon a computer-generated random list into two groups. Group MCI for patients receiving BIS-guided MCI of propofol or Group TCI for patients receiving TCI of propofol.

Once inside the operating room, an intravenous line was secured, all standard ASA monitors were attached including electrocardiogram, noninvasive blood pressure, SpO_2, and BIS monitor. All patients were premedicated with Inj. Midazolam 1 mg IV. General anesthesia was induced after preoxygenation with 100% oxygen for 3 minutes with Inj. Fentanyl 1–1.5 μg/kg, sleep dose of propofol in MCI and as per target plasma concentration in TCI group and nondepolarizing muscle relaxant atracurium 0.5 mg/kg. Propofol Cp50 (blood concentration needed for 50% of subjects to not respond to a defined stimulus) for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 μg/mL.[5-7] We did some pilot cases keeping target propofol concentrations of 3 μg/mL, and we found the BIS values to be in the range of 20 to 25. Therefore, we opted for a target concentration of 2.5 μg/mL. In the MCI group, propofol infusion was titrated to maintain BIS between 40 and 60, and in the TCI group, concentration was fixed at 2.5 μg/mL and BIS values were noted. Analgesia was provided with fentanyl infusion 1 μg/kg/hr. supplemented by fentanyl boluses of 50 μg as rescue analgesia. In the MCI group, if BIS exceeded 60, propofol boluses were given to achieve the desired BIS value.

Fentanyl infusion was stopped approximately 30–40 mins before the end of surgery (at the time of taking out the specimen). Just after the last suture, propofol infusion was also stopped in both groups. The time of point at which propofol was stopped was taken as "time zero" (T0) (Total propofol consumed till this time was measured.). At the end of the surgery, neuromuscular reversal was given with neostigmine and glycopyrrolate in the standard dosage at the appearance of the fourth response to the train of four, and the patient was then assessed for the recovery characteristics in the order of return of spontaneous respiration (T1), response to verbal

commands (T2), extubation (T3), and out of OR (T4). Time was noted from the time of stoppage of propofol, that is, T0 for each characteristic, and compared between two groups.

- Time T0—stoppage of propofol infusion
- Time 1—the return of spontaneous respiration
- Time 2—response to verbal commands
- Time 3—extubation.
- Time 4—shift out of OR.

Return of spontaneous ventilation was assessed by manually feeling the reservoir bag on spontaneous mode with the valve fully open. Response to verbal command was assessed by asking the patient to open their eyes, protrusion of tongue on opening the mouth, and looking for the follow-up of the command. Time was noted when the patient was shifted out of OR. Modified Aldrete score was assigned to each group before shifting the patient out of OR.

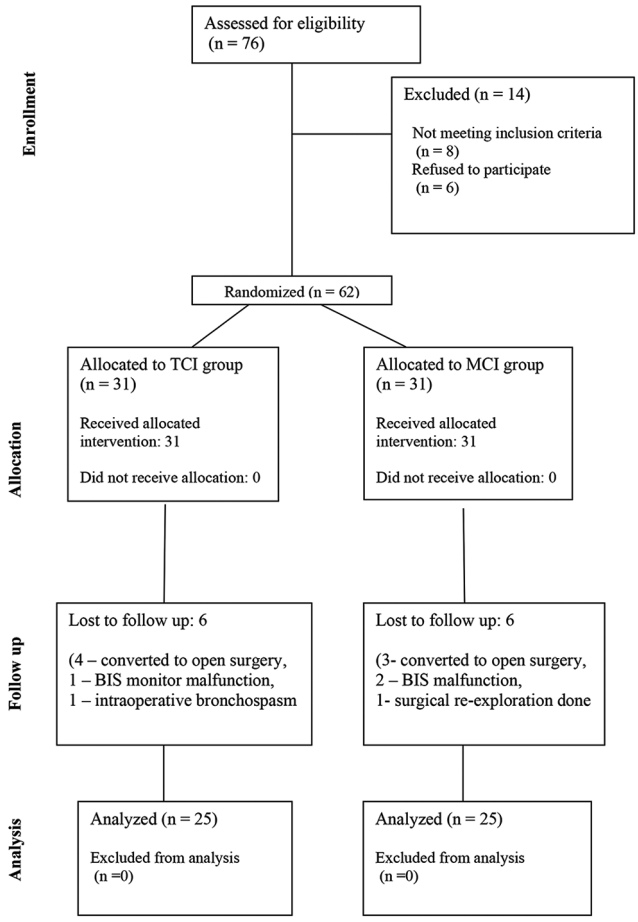
As a secondary objective, the total propofol and fentanyl consumption was noted and analyzed in both groups.

Statistics: All data were collected and tabulated on MS Excel and then analyzed using SPSS Version 16.0 software. Test of normality of data was assessed by the QQ plot. The quantitative variables were expressed as mean ± SD and compared between groups using the unpaired *t*-test. Qualitative variables were expressed in terms of frequencies/percentages and analyzed using the Chi-square test. A P value < 0.05 was considered statistically significant.

Sample size calculation was based on a pilot study done on 10 patients. The mean time to extubation after stopping propofol was 14.1 minutes in the manual group and 17.45 minutes in the targeted infusions group. With the pooled standard deviation of 4.4 units, the study would require a sample size of 28 for each group (i.e., a total sample size of 56, assuming equal group sizes), to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in means between the TCI and MCI group. Assuming a 10% drop-out rate, a total of 62 patients were recruited for the study.

Results

After randomization, there were two groups, the MCI group and the TCI group, of 30 patients each. After a drop out of 10 patients, a total of 50 patients were analyzed, with 25 in each group [Flow chart 1]. There was no statistically significant difference between patients randomized to the MCI or TCI group in terms of age, weight, height, and BMI and therefore were comparable [Table 1]. Duration of surgery was also comparable in both groups [Figure 1].



Flow chart 1: Consort diagram

In the MCI group, it was 228.24 ± 60.43 minutes versus 208.2 ± 29.83 minutes in the TCI group ($P = 0.086$)

Our primary objective was to compare the rates of recovery from anesthesia as measured by four parameters after stopping propofol infusion. We defined time to return of spontaneous ventilation as T1 and noted that it took 8.2 ± 3.83 minutes in the MCI group versus 11.04 ± 9.04 minutes in the TCI group. Similarly, the time to respond to verbal commands was 12.04 ± 5.74 minutes versus 13.08 ± 8.64 minutes. Time to extubation was 14.52 ± 5.59 minutes versus 16.24 ± 9.38 minutes in the TCI group. The time to shift patients out of OR after stopping propofol was also similar at 18.28 ± 6 minutes versus 19.72 ± 9.12 minutes. No difference was noted in any of the times [Table 2]. Recovery, which was defined by all these parameters, was thus found to be statistically similar in both TCI and MCI mode of infusions.

Total consumption of propofol in both groups was also similar at 1168.8 ± 482.19 mg in the MCI group versus 1295.52 ± 311.66 mg (P value = 0.138) in the TCI group. However, on further analysis, when propofol consumption was measured in terms of mg/kg/hr, significantly more

propofol was noted to be consumed in the TCI group at 5.82 ± 0.67 mg/kg/hr versus 4.53 ± 1.0 8 mg/kg/hr in MCI group (*P* value <0.001). Table 3 Consumption of fentanyl in terms of μg/kg/hr in both groups was, however, found to be similar. In the MCI group, fentanyl consumption was 1.21 ± 0.45 μg/kg/hr and in the TCI group, it was 1.19 ± 0.34 μg/kg/hr (*P* value = 0.456; Figure 2).

BIS was monitored in all patients. Average intraoperative BIS values in the MCI group were 48.97 ± 3.75 and that in the TCI group was 34.02 ± 2.6. (*P* value < 0.001), thus significantly better intraoperative BIS values could be obtained with TCI. The BIS values after stopping propofol infusion became statistically similar in both groups Table 4.

As a secondary objective, we monitored a few other parameters. The Aldrete score was assessed before shifting patients into the postoperative ward and there was no difference in the discharge readiness of patients in either group. The Aldrete score was 9.32 ± 0.48 minutes in the MCI group versus 9.24 ± 0.44 minutes in the TCI group.

Table 1: Demographic details of both groups

	MCI *n*=25 Mean	± SD	TCI *n*=25 Mean	± SD	*P*
Age (years)	48.16	±14.12	51.60	±12.6	0.184
Height (cm)	161.32	±8.97	158.80	±5.77	0.122
Weight (kg)	67.28	±11.26	65.05	±11.04	0.242
BMI (kg/m2)	25.89	±4.19	25.92	±4.94	0.489

SD: standard deviation; BMI: body mass index; MCI: manual-controlled infusion; TCI: target-controlled infusion

Table 2: Recovery profiles as assessed by four parameters

	MCI Mean	±SD	TCI Mean	±SD	*P*
T1	8.20 min.	±3.83	11.04 min.	±9.04	0.077
T2	12.04 min.	±5.74	13.08 min.	±8.64	0.309
T3	14.52 min.	±5.59	16.24 min.	±9.38	0.217
T4	18.28 min.	±6	19.72 min.	±9.12	0.256

After cessation of propofol infusion: Time 1—time to return of spontaneous respiration, Time 2—response to verbal commands, Time 3—time to extubation, Time 4—time to shift out of the operating room. MCI: manual-controlled infusion; TCI: target-controlled infusion

Table 3: Propofol and fentanyl consumption

	MCI Mean	±SD	TCI Mean	±SD	*P*
Propofol total dose (mg)	1168.80	±482.19	1295.52	±311.66	0.138
Fentanyl total dose (μg)	298.96	±133.19	260.76	±78.25	0.111
Propofol (mg\kg\hr)	4.53	±1.08	5.82	±0.67	<0.001
Fentanyl (μg\kg\hr)	1.21	±0.45	1.19	±0.34	0.456

SD: standard deviation; MCI: manual-controlled infusion; TCI: target-controlled infusion

Nine patients required rescue analgesia postoperatively, four patients in the MCI group as well as five patients in the TCI group. No patient in either group complained of awareness during surgery.

Discussion

TCI systems usually incorporate propofol and remifentanil algorithms for drug delivery. Remifentanil was not available at our center, thus we used fentanyl infusion at 1 μg/kg/hr. Intermittent boluses were also given as rescue analgesics though, fentanyl consumption was comparable between the two groups and there was no statistical difference observed [MCI group = 1.21 ± 0.45 and in TCI group = 1.19 ± 0.34 μg/kg/hr (*P* value = 0.456)]. This is similar to results reported by Breslin *et al.*[3] where fentanyl consumption was noted to be 3.2 ± 0.8 μg/kg in manual infusion against 3.1 ± 0.8 μg/kg in the TCI group.

The time to recovery assessed by the various clinical parameters was similar in both groups. Return of spontaneous ventilation after stoppage of propofol infusion, time to respond to verbal command, time to extubation as well as time to shifting out of OR from stoppage of propofol infusion was comparable between two groups. Although propofol consumption noted as mg/kg/hr was significantly higher in the TCI group with statistically significant lower values of intraoperative BIS, the recovery characteristics after stoppage of propofol were almost similar and comparable between the two groups. Thus, the intraoperative depth of anesthesia was better maintained by the TCI group with similar recovery times as the MCI group. These findings are in agreement with a study by Russell *et al.*[8] who also observed that despite a significantly greater amount of propofol administration in the TCI group, the times to recovery and orientation were not significantly prolonged compared with the manual group. This is probably due to the

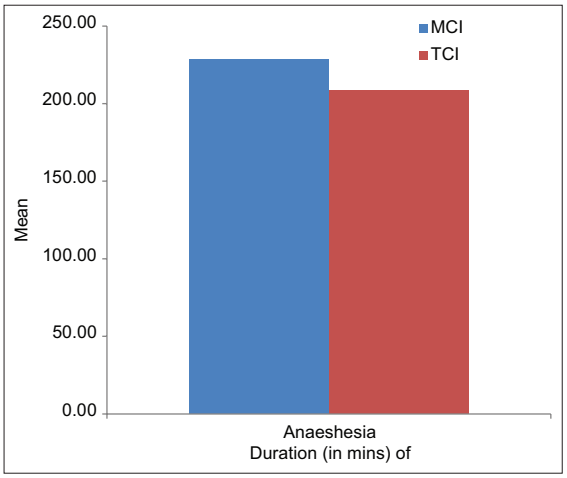


Figure 1: Duration of anesthesia

unique pharmacokinetic and pharmacodynamic properties of propofol, which makes it useful in ambulatory surgeries. The context-sensitive half-time for propofol for infusions of up to 8 hours is less than 40 minutes.[9] Because the required decrease in concentration for awakening after anesthesia or sedation with propofol is generally less than 50%, recovery from propofol remains rapid even after prolonged infusion. A study by Laso *et al.*,[10] however, has reported that patients receiving targeted infusions required lesser doses of propofol thus demonstrated a faster recovery as compared to patients in the MCI group.

In our study, no statistically significant difference was found in the total dose of propofol consumed in both groups. The total dose of propofol in the MCI group was 1168.52 ± 482.19 mg and in the TCI group, it was 1295.52 ± 311.66 mg (*P* value = 0.138). Chan *et al.* observed that BIS-guided anesthesia leads to a 21% reduction in propofol consumption as compared to anesthesia regimen based on clinical parameters.[11] Our findings corroborate with that study, as we also report a lower propofol consumption in the MCI group. This could be a result of careful titration of propofol infusion to maintain BIS in the range of 40–60.[12]

We also observed that patients with TCI showed greater depths of anesthesia with a significant difference in BIS values between the TCI group and MCI group in our study. [TCI group—34.02 ± 2.6 and MCI group—48.97 ± 3.75 (*P* value <0.001)]. This could also be attributed to a higher per kg consumption of propofol in the TCI group at a target concentration of 2.5 mcg/mL. BIS values during the recovery period, that is, after cessation of propofol infusion were analyzed to be similar in both groups. We also noted the Aldrete score before shifting patients into the postoperative ward.[13] As the recovery profiles were statistically similar, we cannot expect the Aldrete score to be much different. Indeed, in the MCI group, it was noted to be 9.32 ± 0.48 minutes versus 9.24 ± 0.44 minutes in the TCI group (*P* value = 0.269)]. Values more than 9 indicate good recovery in both groups and are considered adequate for the discharge of patients [Table 5].

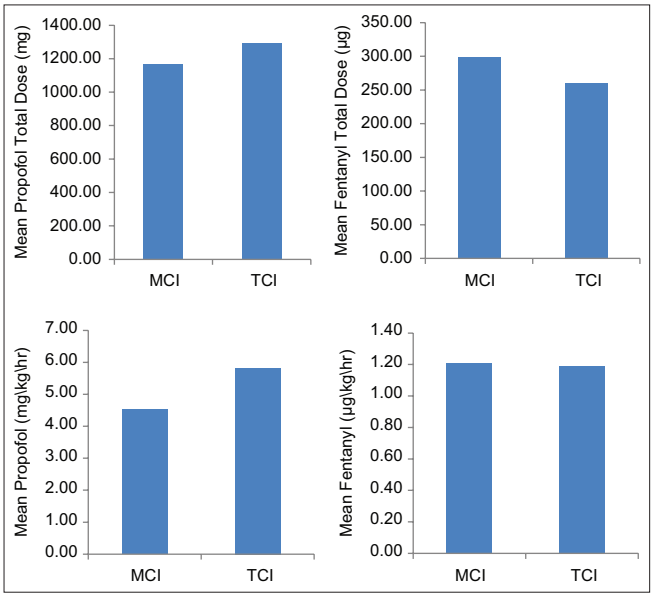


Figure 2: Propofol and fentanyl consumption

Conclusion

Recovery from anesthesia is similar when using TIVA with propofol and Fentanyl, either by the MCI method or TCI method. TCI results in greater depths of anesthesia though per kg/min consumption of propofol may be more with TCI.

Limitations of the Study

This was a single-center study catering only to cancer patients thus results may not be generalized to the general population.

Table 4: BIS values during recovery

	MCI Mean	±SD	TCI Mean	±SD	*P*
BIS T0	53.64	±7.75	47.68	±13.95	0.034
BIS T1	70.56	±6.34	70.52	±8.69	0.493
BIS T2	79.20	±5.81	78.88	±8.36	0.438
BIS T3	85.12	±5.09	85.68	±7.14	0.375
BIS T4	92.16	±4.05	91.12	±5.14	0.215

BIS: bispectral index; SD: standard deviation; MCI: manual-controlled infusion; TCI: target-controlled infusion

Table 5: Modified Aldrete Score

Criteria	Point value
Oxygenation	
SpO_2 >92% on room air	2
SpO_2 >90% on oxygen	1
SpO_2 <90% on oxygen	0
Respiration	
Breathes deeply and coughs freely	2
Dyspneic, shallow or limited breathing	1
Apnea	0
Circulation	
Blood pressure±20 mmHg of normal	2
Blood pressure±20–50 mmHg of normal	1
Blood pressure more than±50 mmHg of normal	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responsive	0
Activity	
Moves all extremities	2
Moves two extremities	1
No movement	0

SpO_2: Peripheral oxygen saturation

Target drug concentrations were fixed in the TCI group based upon our pilot study, thus inter-individual variations cannot be accounted for. There may also have been some errors of loop defects in TCI.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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