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Comparison of target controlled infusion and manual infusion of propofol for sedation in spinal anesthesia

Gülten Arslan* and Özlem Sezen

Abstract

Objective: The purpose of this study was to compare the quality of sedation during surgery under spinal anesthesia with propofol using target-controlled infusion versus manual infusion regarding sedation, hemodynamics, recovery pattern, and patient and surgeon satisfaction.

Subjects and methods: This prospective randomized controlled study was performed on 60 ASA I–III patients enrolled for elective surgery under spinal anesthesia. They received propofol infusion for intraoperative sedation using target-controlled infusion or manually. The target-controlled infusion group ($n = 30$) received propofol with the target-controlled infusion system (Schnider's model) with the initial target plasma concentration set at 1.5 μg ml^{-1}. The manual infusion group ($n = 30$) received propofol manually in a bolus of 0.5 mg kg^{-1} and in maintenance doses of 1.5 mg kg^{-1} h^{-1}. In both groups, the anesthesiologist adjusted to increase or decrease the infusion rate by 0.2 μg ml^{-1} to maintain an Observer's Assessment of Alertness and Sedation Scale of 3–4. We recorded the amount of propofol, hemodynamics, sedation scores, VAS, BIS, patient's and surgeon's satisfaction, recovery pattern, and side effects.

Results: Compared with the manual infusion group, the target-controlled infusion group had a faster time to reach OAAS/3 (7.2 ± 3.47 min for the target-controlled infusion group vs 5.8 ± 1.50 min for the manual infusion group; $p = 0.04$) and recovery time (5.1 ± 1.70 min vs 3.6 ± 1.09 min; $p < 0.001$); deeper BIS levels in the 10th, 20th, and 30th minutes ($p = 0.04$, $p = 0.03$, $p = 0.05$); and deeper Observer's Assessment of Alertness and Sedation Scale in the 10th and 40th minutes ($p = 0.05$, $p = 0.03$), and more surgeon's satisfaction ($p = 0.05$).

Conclusion: It was concluded that propofol at the same doses administered with target-controlled infusion for sedation during spinal anesthesia could be preferred due to faster sedation and recovery and more patient's satisfaction compared to manual infusion.

Introduction

The main advantages of regional anesthesia for anesthesiologists are stability of the respiratory and circulatory system, patient consciousness, oral communication, postoperative rapid recovery, and preservation of protective airway reflexes (Asehnoune et al., 2000). Sedation in regional anesthesia helps to make the surgery more suitable for the patient, anesthesiologist, and surgeon. Generally, minimal or moderate sedation is preferred, which allows for verbal communication between the anesthetist and the patient during the surgical procedure.

The aims of sedation are to ensure the safety and well-being of the patient, to minimize the discomfort by providing anxiolysis, amnesia, and analgesia; to ensure that there is behavior and movement control that will allow for the surgical procedure to be completed safely; and to bring the patient safely to discharge (Höhener et al., 2008).

Propofol is commonly used for conscious sedation during local or regional anesthesia due to its

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pharmacological properties such as rapid onset of action, rapid change of sedation level, early recovery, excellent amnesic effect, and low incidence of nausea and vomiting (Triantafillidis & Merikas on P, E, Nikolakis D, Papalois AE., 2013). Propofol infusions are administered by a repeated bolus application, manual controlled infusion (MCI), or target-controlled infusion (TCI).

Sedation with single or repeated doses may lead to issues such as unstable blood and target organ concentrations, undesirable effects, variable sedation levels, and hemodynamic side effects. Since the application of continuous infusion following the loading dose (manual infusion, MI) will lead to an increased blood concentration over time, the infusion rate should be changed intermittently to maintain the desired level of sedation. This problem can be eliminated by applying TCI. In TCI, a microprocessor adjusts the infusion rate according to the algorithms based on pharmacokinetic models (Struys et al., 2016; Leslie et al., 2008). The advantages of TCI are that the concentration of the sedative agent in the target area reaches equilibrium more rapidly, the maintenance of equilibrium is easier, and if a sedation level change is desired, a new equilibrium can be reached faster and easier.

The aim of this study was to compare the quality of sedation during surgery under spinal anesthesia with propofol used by MI versus TCI regarding the Bispectral Index Scale (BIS) values and Observer's Assessment of Alertness and Sedation (OAAS) scale hemodynamics, recovery pattern, and patient and surgeon satisfaction. The study was designed to investigate the hypothesis that propofol by TCI is associated with a shorter recovery and faster desired level of sedation time when compared with MI.

The primary endpoint was faster desired level of sedation time, while the secondary endpoints were recovery time, propofol doses, satisfaction, and more common usability in clinical anesthetic practice by TCI when compared with MI.

Materials and methods

This prospective, randomized study was conducted in the university-affiliated tertiary referral hospital after approval from the Institutional Ethics Committee (2018/514/129/2). After written informed consent from each patient, 60 American Society of Anesthesiologists (ASA) physical status class I–III patients, aged 20–90, scheduled for elective urologic surgery lasting more than 30 min were enrolled. Patients with a hypersensitivity to soybean, egg, neuropsychiatric disorders, kidney or liver failure, chronic treatment with opioids, sedatives, pregnancy-lactation, and obesity (BMI > 30) were excluded from the study.

The patients were one-to-one randomized into two groups: the MI and TCI group, using the method of drawing lots from an envelope with an equal number of papers on which the group is indicated. The patients did receive any premedication. In the operation room, intravenous infusion of isotonic saline solution (8 ml/kg/h) was started. Heart rate (HR), non-invasive blood pressure, and peripheral oxygen saturation (SpO_2) were continuously monitored and recorded at pre-spinal, post-spinal, and pre-sedation, and at 10-min intervals until the end of the operation. BIS values were recorded with BIS monitor and sensor [(INVOS™ 5100C) (Covidien, CO, USA)] (BIS™, Covidien) used to determine the depth of sedation after cleaning the forehead with alcohol. Spinal anesthesia was performed by intrathecal injection of 12.5 mg 0.5% hyperbaric bupivacaine with a 25-gauge spinal needle in between L3 and L4.

The patients in the TCI group (n = 30) received propofol (Diprivan, Astra Zeneca, Stockholm, Sweden, 20 mg/ml) with a TCI pump (Injectomat TIVA Agilia®, Fresenius Kabi, France), (Fig. 1) according to Schnider's model, with the initial target plasma concentration set at 1.5 μg/ml. The MI group (n = 30) received propofol with the same pump in a bolus of 0.5 mg/kg and in maintenance doses of 1.5 mg/kg/h. The titration speed of propofol was adjusted by increasing or decreasing the blood concentration of propofol by 0.2 μg/ml according to the OAAS scale of 3-4 (OAAS/3-4) during surgery in both groups. In our study, drug dosages were determined after literature review. Administrations of propofol were stopped at the end of the operation.

Age, gender, weight, height, ASA class, sedation time, surgery time, total dose of propofol, time to reach OAAS/3-4, and recovery time (from the discontinuation of propofol infusion until adequate response to verbal command was regained or OAAS/5) were all recorded. Mean arterial pressure (MAP), HR, SpO_2, BIS, OAAS scale, visual analog scale (VAS) (pain scale), and anxiety scale at pre-spinal, post-spinal, pre-sedation, and the 5th minute after sedation, then 10-min intervals until the end of the operation; surgeon's and patient's satisfaction; and side effects (pain on injection, nausea and vomiting,

Fig. 1 Injectomat TIVA Agilia®, Fresenius Kabi, France

bradycardia (HR < 50 beats/min), desaturation (SpO_2 < 90%), agitation) were evaluated by an anesthesiologist who was blinded to the propofol infusion protocol. Oxygen was supplemented with a face mask (2 l/min). When SpO_2 was < 90, airway was placed and oxygen was increased to 4 l/min. When the heart rate was < 50 beats/min, 0.01 mg/kg of atropine was administered.

The Observer's Assessment of Alertness and Sedation (OAAS) scale and anxiety scale are defined in (Tables 1 and 2) (Hong et al., 2003; Ramsay et al., 1974).

The patient's and surgeon's satisfaction was assessed using a 5-point verbal scale (excellent, very good, good, fair, poor) for comfort by an observer who was blinded to the protocol of the study (Joshi et al., 2015).

Statistical analysis

The demographic characteristics of the patients and their collected data were entered in Statistics version 25 of IBM® SPSS®. Variables were characterized using mean, maximum, and minimum values, and percent values for qualitative variables were used. Normal distributions were reported as mean ± SD and Student *t* test was used for comparisons between groups. Pearson chi-square test was used for the analysis of qualitative variables, and Fisher's exact test was used if the group was small. Nonparametric continuous variables were recorded as median and intermittent distributions and compared using Mann-Whitney *U* tests. $p < 0.05$ was considered statistically significant.

Sample size was determined using the sample size formulas. Sixty patients from 150 patients in the same time period were included in the study. Therefore, the confidence level was 95% (alpha value 5%) and the level of precision 10%.

Results

Sixty patients in total were scheduled in the study, and 30 of them were allocated to each of the two groups. The clinical characteristics of patients were similar in both groups and are shown in (Table 3).

Among the groups, there were no significant differences in sex, age, height, weight, ASA score, and duration of sedation and surgery (Table 3). Total doses of propofol were similar in the two groups: 188.2 ± 80.2 mg and 180.7 ± 53.4 mg, for the MI and TCI groups, respectively ($p = 0.630$). On the other hand, the time to reach OAAS/3-4 was longer in the MI group ($p = 0.04$). Recovery time was also observed statistically longer in the MI group ($p > 0.001$) (Table 3).

When the pre and post-spinal values were examined, there were no statistically significant differences between the groups in MAP, HR, SpO_2, BIS, and OAAS scale.

With respect to hemodynamic changes, the MAP decreased significantly in the TCI group only at the 20th minute ($p = 0.001$) during surgery (Fig. 2). HR and SpO_2 showed no significant differences between the groups (Figs. 3 and 4).

At the 10th, 20th, and 30th minutes of the BIS score, a significant difference was observed among the groups ($p = 0.04$, $p = 0.03$, $p = 0.05$, respectively). The difference in the 40th-minute BIS score was also close to the level of significance ($p = 0.07$). It was determined that BIS in the TCI group was significantly lower at this time in comparison to the MI group (Fig. 5).

OAAS scales during surgery were lower in the TCI group overall. Specifically, OAAS at the 10th minute ($p = 0.05$) and 40th minute ($p = 0.03$) was significantly lower in the TCI group in comparison to the MI group (Fig. 6).

Table 1 Observer's Assessment of Alertness and Sedation (OAAS) scale (Hong et al., 2003)

Scale	Alertness degree
5	Fully awake
4	Drowsy
3	With eyes closed, but responsive to verbal stimulation immediately
2	With eyes closed, only responsive to physical stimulation
1	No response to physical stimulus

Table 2 Anxiety scale (Ramsay et al., 1974)

Scale	Patient state
1	Anxious, uncooperative
2	Completely cooperative, emotional change
3	Cooperative, full readiness to operation

Table 3 Clinical and procedural characteristics of the patients

	Target-controlled infusion (*n* = 30)	Manual infusion (*n* = 30)	*p*
Age, mean ± SD (years)	54.9 ± 14.3	56.5 ± 15.3	0.685
Sex, (male/female)	23/7	23/7	Na
Height, mean ± SD, (cm)	169.5 ± 4.1	170.9 ± 6.9	0.326
Weight, mean ± SD, (kg)	79.6 ± 11.8	80.2 ± 15.0	0.857
ASA class (1/2/3)	8/13/19	3/19/8	0.449
Duration of sedation, mean ± SD (min)	64.6 ± 12.3	68.2 ± 20.5	0.891
Duration of surgery, mean ± SD (min)	61.0 ± 11.4	63.2 ± 20.3	0.756
Total dose of propofol, mean ± SD (mg)	180.7 ± 53.4	188.2 ± 80.2	0.630
Time to reach OAAS/3-4, mean ± SD (min)	5.8 ± 1.5	7.2 ± 3.47	**0.04**
Recovery time, mean ± SD (min)	3.6 ± 1.09	5.1 ± 1.7	**< 0.001**

Na not applicable

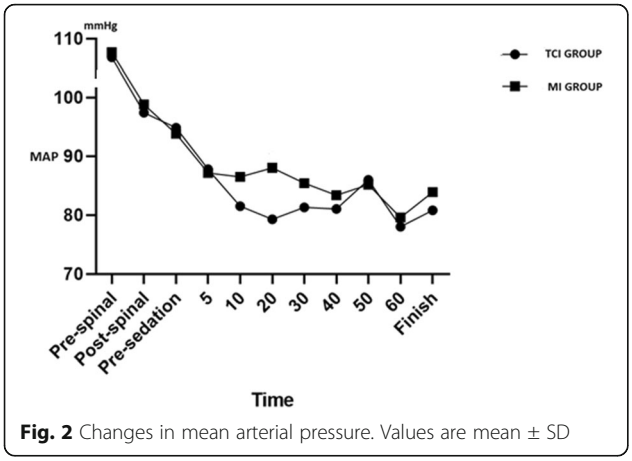

Fig. 2 Changes in mean arterial pressure. Values are mean ± SD

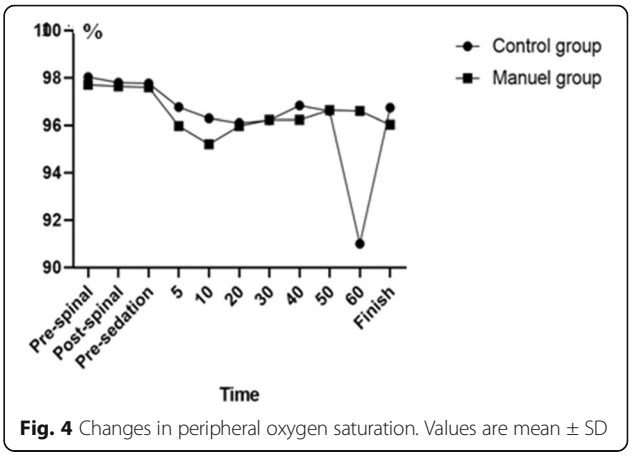

Fig. 4 Changes in peripheral oxygen saturation. Values are mean ± SD

The values of VAS of all patients after and before spinal puncture were zero. We did not observe significant differences in these variables in follow-up after sedation with the two groups (Fig. 7). Anxiety scale was 3 before spinal puncture for both groups. There was no difference between the groups during surgery (Fig. 8).

With respect to patient and surgeon satisfaction during surgery, patient satisfaction showed no significant differences between the groups. On the other hand, in the TCI group, we found differences in surgery satisfaction not statistically significant, but close to significant (p = 0.05) (Table 4). No statistically significant difference was found between the groups in terms of side effects (pain on injection, nausea-vomiting, bradycardia, desaturation, agitation) (Table 5). None of the patients required assisted ventilation with bag mask or endotracheal intubation.

When the need for a change in the propofol rate during surgery is examined, patients in the TCI group were found to have less intervention than those in the manual group (53.3% vs 73.3%), but the difference was not statistically significant (p = 0.108). In the TCI group, the intervention was in the form of a 16.7% dose increase and 10% dose reduction, whereas the values in the manual group were a 33.3% increase and 13.3% decrease, respectively (p = 0.252).

Discussion

Although there are many advantages of regional anesthesia, it is a disadvantage for patients to remember the operation. This issue can be eliminated by sedation, which provides amnesia, anxiolysis, and even a little analgesia. However, sedation during regional anesthesia should not depress the hemodynamic parameters and breathing and should not prolong the recovery while increasing patient and surgeon comfort and supporting for insufficient anesthesia. For continuous infusion, the properties expected from intravenous anesthetic agents are that they are water soluble and have few side effects, reasonable cost, rapid onset and termination of action, a lack of drug accumulation, and inability of metabolites (Miller, 1994). Propofol is the most suitable agent for continuous infusion due to the fact that it has all of these required (Kim & Sohn, n.d.). Another critical concern for anesthesiologists is not just the drug but the method of administration for the selected medication.

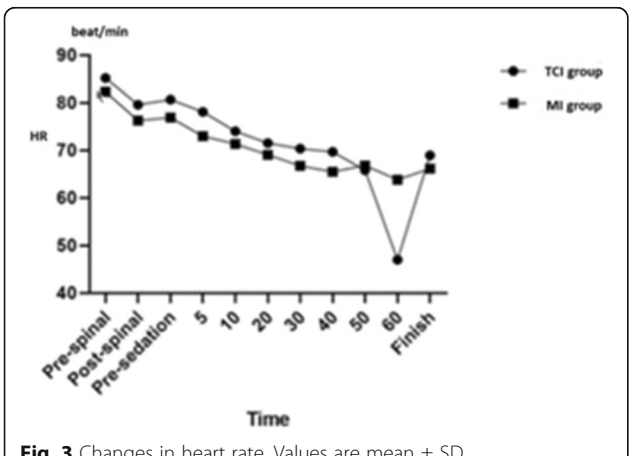

Fig. 3 Changes in heart rate. Values are mean ± SD

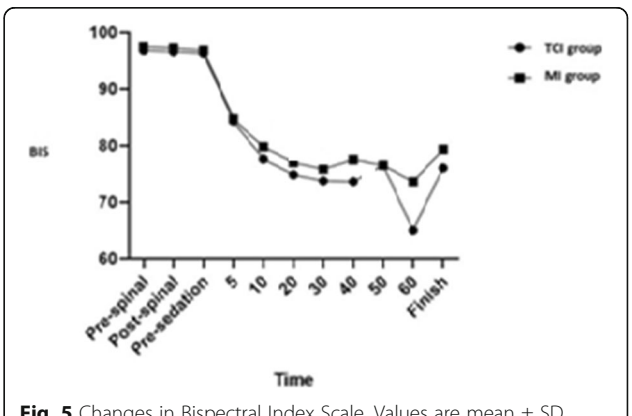

Fig. 5 Changes in Bispectral Index Scale. Values are mean ± SD

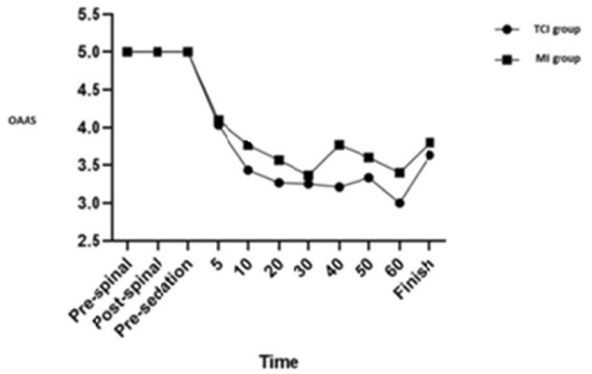

Fig. 6 Changes in Observer's Assessment of Alertness and Sedation. Values are mean ± SD

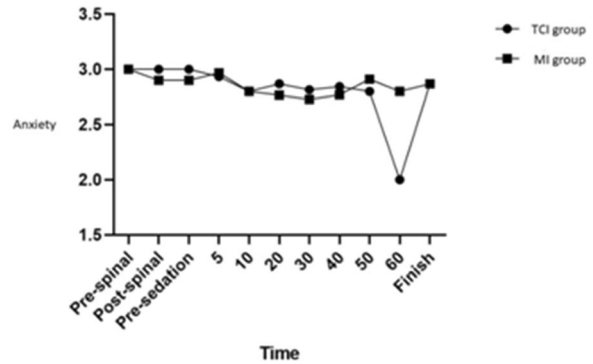

Fig. 8 Changes in anxiety scale. Values are mean ± SD

The TCI of propofol, which is widely used for this purpose, is an alternative to the MI method (Leslie et al., 2008). Although there are many studies about these two different infusion systems, there is disagreement in the literature about the superiority of each method over the other. Therefore, we aimed to compare two different infusion methods (MI-TCI) of propofol for sedation during spinal anesthesia.

Marsh and Schnider pharmacokinetic models are available for propofol to be used in target-controlled infusion. Although the Schnider model for effect site concentration (Ce)–targeted infusion is not popular (as it incorporates age, height, weight, and lean body mass), it has advantages of avoiding excessive overshoot or undershoot of blood concentrations around Ce due to a smaller volume of distribution. It would be more suitable in the patients who have a lower lean body mass and would require lesser doses of propofol for induction and maintenance of a constant plasma concentration. For these reasons, we preferred to use the Schnider model in our study.

In studies comparing TCI and MI methods, there are studies showing that the TCI method is more advantageous in terms of drug consumption (Triem et al., 2006; Laso et al., 2016), as well as studies that show more drug consumption (Leslie et al., 2008; Breslin et al., 2004; Russell et al., 1995; Lehmann et al., 2002), or there is no significant difference between the two groups (Vucicevic et al., 2016). We believe that these differences are probably due to the infusion duration of drugs, because TCI applications were associated with higher initial infusion rate of propofol (usually 20–30 min). Over time, the rate of infusion decreases and reverses in long-term applications in the TCI group. Therefore, infusion duration in the TCI system affects the amount of drug consumption.

As a result of these facts, in TCI, more propofol use in short-term applications and less propofol use in long-term applications when compared with MI were observed. In our study, in relation to the consumption of propofol, there were little differences between the groups in terms of TCI superiority. However, the observed small differences were not statistically significant (Table 3). Similar results to ours have been reported by Laso et al. (2016), Vucicevic et al. (2016), and Müller et al. (2010). We believe that the reason for not observing

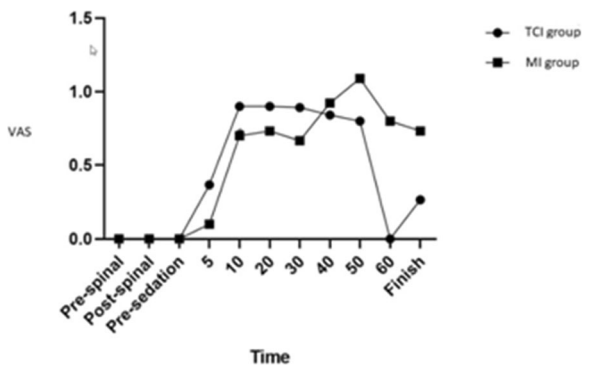

Fig. 7 Changes in visual analog scale. Values are mean ± SD

Table 4 Satisfaction of patient and surgeon during surgery

	Target-controlled infusion (n = 30)	Manual infusion (n = 30)	p values
Patient's satisfaction			
Excellent	25 (83.3%)	22 (73.3%)	0.270
Good	4 (13.3%)	5 (16.7%)	
Fair	1 (3.3%)	3 (10.0%)	
Poor	0 (%0)	0 (%0)	
Surgeon's satisfaction			
Very good	28 (93.3%)	23 (76.7%)	**0.05**
Good	2 (6.7%)	5 (16.7%)	
Not bad	0 (%0)	2 (6.7%)	
Poor	0 (%0)	0 (%0)	

Table 5 Incidences of perioperative side effects

	Target-controlled infusion (n = 30)	Manual infusion (n = 30)	p values
Pain on injection	16 (53.3%)	13 (43.3%)	0.438
Nausea-vomiting	1 (3.3%)	--	Na
Bradycardia	3 (10.0%)	2 (6.7%)	0.640
Desaturation (SpO_2 < 90%)	5 (16.7%)	5 (16.7%)	Na
Agitation	2 (6.7%)	6 (20.0%)	0.129

Na not applicable

different statistically significant values in terms of propofol consumption between the groups may be duration of sedation (> 30 min, but neither too short nor too long as our study, our sedation duration 66.4 min).

TCI system infuses the drug rapidly until it reaches the specified target concentration. It then determines the infusion rate needed to maintain this level. In our study, OAAS scale was used to assess the degree of sedation. The time to reach the desired level of sedation (OAAS/3-4) was observed to be shorter in the TCI group in agreement with the studies of Russell et al. (1995) and Laosuwan et al. (2011).. Although there is no difference between the amount of propofol consumed, we believe that the higher initial infusion rate in the TCI system may explain this, although this result seems contradictory. Propofol infusions were titrated to achieve an adequate depth of anesthesia using clinical parameters. When the OAAS scales were evaluated, the values were lower in the TCI group at the 10th and 40th minutes and the difference between the two groups was statistically significant. In the beginning of this Schnider model TCI, we think that it may be due to high propofol use especially in the first 30 min. Laosuwan et al. also reported that the number of patients whose OAAS scale was less than 3 was higher in the TCI group (Laosuwan et al., 2011). BIS values are also compared, these values were recorded 60–80 in both groups, while the OAAS/3-4 in TCI and MI during surgery. These results suggest that BIS may also show the degree of sedation. In our study, similar to the results of Breslin et al. (2004) and Mu et al. (2017), BIS scores were lower in the TCI especially at the 10th, 20th, and 30th minutes (Fig. 5). The difference in the total dosage of propofol was mainly due to a higher rate of propofol administration in the first 30 min in the TCI group.

Initial administration of high doses of propofol in TCI may affect hemodynamic parameters. However, in our study, MAP decreased significantly in the TCI only at 20 min, unlike the MI. Laosuwan et al. (2011) also reported that MAP of the TCI group was significantly lower than the MCI group at the 15th, 30th, and 45th min. In contrast, Vucicevic et al. reported that the MI group had a lower MAP at the 10th minute after the sedation in colonoscopy (Vucicevic et al., 2016). In our study, we believe that the decrease in MAP in 20 min is due to higher use of propofol in the TCI system during the initial 30 min. Other hemodynamic parameters were similar in the groups.

As a result, due to the high blood concentration of the propofol infusion rate in the first 20–30 min in the TCI group, we can say that the hemodynamic parameters are low, but among the acceptable values.

The use of TCI was associated with a significantly shorter time of recovery in our study. Laso et al., Müller et al., and Passot et al. also reported that recovery time in the TCI group was significantly shorter than the manual group (Laso et al., 2016; Müller et al., 2010; Passot et al., 2002). In their study, Müller et al. reported that shorter recovery time would also enable more effective use of the operating room (Müller et al., 2010). Although the total amount of propofol consumed was similar in both groups, we think that the recovery time may be shorter in operations lasting more than 30 min as in our study, as the drug infusion rates decreased significantly after the first 20–30 min in the TCI system.

There was no patient who complained of pain in both groups during the surgery in our study. There was no significant difference between the groups in terms of VAS, anxiety scores, patient's satisfaction, and side effects, but a difference in surgeon's satisfaction was determined in that TCI was associated with more surgeon satisfaction. Similar results to ours have been reported by Leslie et al. (2008), Laso et al. (2016), and Müller et al. (2010).

Leslie et al. in agreement with our results found that the TCI method required less dose adjustment during anesthesia than the MI method, but there was no significant difference between the groups in terms of anesthesia quality and side effects (Leslie et al., 2008).

Limitations

BIS is the best available objective guide to depth of anesthesia. The BIS was recorded every 10 min manually. Using a computer program with continuous recording of BIS data would allow a more precise and accurate estimation of performance of both techniques. Similarly, OAAS was recorded every 10 min. In addition, the number of cases could be increased. More comprehensive studies are needed for this.

Total intravenous anesthesia has been widely used in our country with manual infusion for many years. Although we are a large university hospital in which all operations are performed, we believe that target-controlled infusion, which is not a new application, is not used equally. Based on the literature reviews and especially the data obtained from our study, we believe that this

infusion technique, with its many advantages, will be more widely used in our clinic.

Conclusion

Although the same doses of propofol are used for sedation in spinal anesthesia, it was concluded that it can be preferred in the TCI compared to MI because of providing more effective and faster sedation and recovery, and surgical satisfaction and therefore it can be used more widely in our clinics.

Abbreviations

MCI: Manual controlled infusion; TCI: Target-controlled infusion; MI: Manual infusion; OAAS: Observer's Assessment of Alertness and Sedation; ASA: American Society of Anesthesiologists; HR: Heart rate; SpO_2: Peripheral oxygen saturation; BIS: Bispectral Index Scale; OAAS/3-4: OAAS scale of 3-4; MAP: Mean arterial pressure; VAS: Visual analog scale

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Authors' contributions

GA and OS contributed to the conception and design of the study. GA and OS collected the data. GA analyzed and interpreted the data. GA and OS participated in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This prospective randomized controlled clinical trial was conducted after approval of the Kartal Dr. Lutfi Kırdar Training and Research Hospital Ethics Committee (decision no. 2018/514/129/2) and written informed consent of all the participants, according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper. The authors declare that they have no conflict of interest to the publication of this article.

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