

*Original Article***Target-controlled infusion of remifentanil with propofol or desflurane under bispectral index guidance: quality of anesthesia and recovery profile**

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Abstract

BACKGROUND: Our objective was to examine the clinical properties of two anesthetic regimens, propofol target-controlled infusion (TCI), or desflurane using remifentanil TCI under bispectral index (BIS) guidance during ear, nose, and throat (ENT) procedures.

METHODS: Forty consenting patients who scheduled for ENT procedures were prospectively studied and were included in one of the two groups: TCI group or desflurane (DES) group. General anesthesia was induced with 3 ng mL⁻¹ and 4 µg mL⁻¹ effect site concentrations (Ce) of remifentanil and propofol, respectively, with TCI system. After intubation, while propofol infusion was continued in the TCI group, it was ceased in the DES group and desflurane with an initial delivered fraction of 6% was administered. The Ce of propofol infusion and inspired fraction of desflurane was adjusted in order to keep BIS as 50 ± 10.

RESULTS: General mean values of mean arterial pressure (MAP) and heart rate (HR) for the TCI group was significantly higher than DES group (89.3 mmHg and 72.4 bpm vs. 77.1 mmHg and 69.5 bpm). Early emergence from anesthesia did not significantly differ between the groups. The rate of patients' Aldrete score (ARS) to reach 10 was found to be 100% at the 15th min in both groups.

CONCLUSIONS: Bispectral index guided combinations of remifentanil TCI either with propofol TCI or desflurane anesthetic regimens are both suitable for patients undergoing ENT surgery. The lower blood pressure in the remifentanil TCI with desflurane anesthetic regimens may be a significant advantage.

KEYWORDS: Infusion Pumps, Remifentanil, Propofol, Desflurane, Consciousness Monitors.

JRMS 2011; 16(5): 611-620

The availability of rapid and shorter-acting intravenous and volatile anesthetics has facilitated early recovery in most operational settings. In this respect, both propofol and desflurane are suitable agents for maintenance of anesthesia during ear, nose, and throat (ENT) procedures because of their favorable pharmacological properties.¹ The target-controlled infusion (TCI) system is an anesthetic dosing technique that was developed during the last decade and is becoming increasingly popular in anesthesia departments.² Propofol and remifentanil are a valuable combination for TCI because of their simi-

lar properties including rapid onset and short action time.³

There are many studies looking at propofol anesthesia versus desflurane anesthesia.^{1,4-10} However, to our knowledge, there are no published reports comparing desflurane anesthesia and propofol TCI anesthesia in combination with remifentanil TCI. Bispectral index (BIS) was proved to be useful for measuring the depth of anesthesia.¹¹⁻¹⁵ One of the problems of those studies is that the depth of anesthesia is determined according to weaker criteria instead of using BIS monitoring for guiding administration of anesthesia.^{4,16} Therefore, our

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objective was to examine the clinical properties, specifically in terms of recovery profile and postoperative side effects, of the two anesthetic regimens using remifentanil TCI with either propofol TCI system or desflurane under BIS guidance during ENT procedures.

Methods

Following the approval of the study by institutional ethics committee, informed consent was obtained and 40 patients classified as American Society of Anesthesiologists physical status (ASA) I-II scheduled for ENT procedures were enrolled in this prospective study. The surgical procedures involved were septoplasty, polypectomy, endoscopic sinus surgery, rhinoplasty, nasal reconstructive surgery, or a combination thereof. The surgeries were not performed by the same surgeon; however, the surgeons who performed the surgeries had close seniorities. Patients aged 18-65, who did not receive any sedative or analgesic drugs for 24 hours before surgery, and patients who were not significantly hypertensive (diastolic blood pressure ≥ 100 mmHg) or hypotensive (systolic blood pressure ≤ 100 mmHg), or who did not present any previous signs of bradyarrhythmic heart disorders were included in the study. Patients were randomly allocated into two groups according to computer generated group numbers as TCI group or DES group corresponding to administration either propofol/remifentanil TCI (TCI group; $n = 20$) or an inhalational anesthetic regimen using desflurane/remifentanil (DES group; $n = 20$). Before the operation, patients were taught to evaluate their pain according to a numeric rating scale (NRS) on an 10 point pain scale, where 0 corresponds to "no pain" while 10 means "worst possible pain". Numeric rating scale between 0 and 3 was accepted as considerably painless.

No premedication was given. Standard monitoring included electrocardiogram, non-invasive blood pressure, pulse oximetry (SpO_2) and end-tidal carbon dioxide ($ETCO_2$). The Quatro Sensor electrodes were placed on foreheads and BIS values were displayed using an Aspect electroencephalogram monitor (A-2000

BIS XP Platform; Aspect® Medical Systems, Newton, USA). Muscle relaxation was monitored with a train-of-four nerve stimulator (TOF Watch SX; Organon, Ireland). Measurements obtained preoperatively that is, one minute after the induction (beginning of propofol infusion); when loss of consciousness (LOC) was confirmed through loss of eyelid reflex and verbal contact; the 1st and 5th minutes after tracheal intubation; 1, 5 and 10 minutes after incision; and then with 10 minute intervals and at tracheal extubation, were recorded. The records of patients were also followed up and kept at the post-anesthesia care unit (PACU). On arrival in the operating room, the baseline values for BIS, heart rate (HR), mean arterial pressure (MAP), and SpO_2 were obtained, and an intravenous catheter was placed. Before induction of anesthesia, patients were given 5 mL kg^{-1} intravenous isotonic solution and then breathed 100% oxygen for 5 minutes.

Propofol and remifentanil were administered with a TCI device (Orchestra Base Primea®, Fresenius Kabi, France). Syringes of 1% propofol (10 mg/mL) and remifentanil (50 $\mu g/mL$) were simultaneously loaded on the device and connected to the patient's intravenous catheter using a three-way stopcock. The pharmacokinetic models of Schnider et al¹⁷ and Minto et al^{18,19} were both used. General anesthesia was induced with 3 $ng mL^{-1}$ and 4 $\mu g mL^{-1}$ effect site concentrations (C_e) of remifentanil and propofol, respectively. These drug doses were determined by a previous study.²⁰ After LOC, the TOF monitor was switched on and tracheal intubation was facilitated with rocuronium bromide 0.6 $mg kg^{-1}$. All patients were ventilated with a fresh gas flow of 4 $L min^{-1}$ of oxygen (50%) and air (50%) mixture to maintain $ETCO_2$ between 30 and 35 mmHg (Dräger®, Julian Plus, Germany). Analgesia was maintained with remifentanil concentration at a C_e of 3 $ng mL^{-1}$. After intubation, for maintenance of hypnosis, while propofol infusion was continued in the TCI group, it was ceased in the DES group and desflurane with an initial delivered fraction of 6% was

administered. During the surgery, while the propofol target concentration was adjusted in increments of $0.5 \mu\text{L}^{-1}$ (increased or decreased), inspired fraction of desflurane was adjusted in increments of 1% volume (increased or decreased) in order to keep BIS value at 50 ± 10 .²¹ Muscle relaxation was supplemented if required (with the aim of maintaining at least one twitch using the train-of-four monitor) with 0.05 mg kg^{-1} rocuronium bromide. Hypotension (a decrease in MAP of more than 20% of the baseline value) was treated first with fluid administration, and then with a small bolus of ephedrine. Bradycardia ($\text{HR} < 50 \text{ bpm}$) was treated with intravenous atropine. If the patient did not respond to this treatment, the level of TCI remifentanyl was decreased or the infusion was discontinued completely. However, if hypertension occurred when the BIS value was between 40 and 60 the level of TCI remifentanyl was increased.

At the end of surgery, all anesthetics were discontinued without tapering and the lungs were ventilated with 100% oxygen at a fresh gas flow of 6 L min^{-1} . The patients were extubated when adequate spontaneous ventilation and response to verbal command were established. The duration of anesthesia was defined as the period from the start of anesthesia induction to the discontinuation of all the anesthetic drugs. Surgery time was defined as the period from the start of the surgery to the end of the surgery. Emergence from anesthesia was assessed as the time from the end of operation until the time of orientation (recalling name and date of birth). During the emergence time, times of returning to spontaneous ventilation, eye opening, tracheal extubation, responding to verbal commands (such as hand squeezing), and orientation were recorded. Thereafter, the patients were directly transferred to the PACU, where further follow-up was done by an independent, blinded observer, who was unaware of anesthesia regimen administered. Post-anesthesia recovery was scored for PACU discharge eligibility using the Aldrete Recovery Scoring (ARS). Criterion for discharge from PACU was defined as ARS greater than 9. Dur-

ing the observation period in the PACU, hemodynamic parameters were recorded as well as side effects such as postoperative nausea and vomiting (PONV).

Patients were asked every 5 min until discharge from PACU to indicate pain experience on the NRS. Postoperative pain greater than 3 on the NRS and shivering was treated with intramuscular 1 mg kg^{-1} meperidine, and also emesis was treated with intravenous 10 mg metoclopramide. The patients were visited in the clinic postoperatively and asked whether they had any problems regarding pain and anesthetic management, and whether they experienced recall of intra-operative events.

Statistical Analysis

Twenty patients per treatment group were necessary to detect a reduction of 15% in the mean levels of the characteristics of emergence from anesthesia with a level of significance of p values < 0.05 and a statistical power of 0.90. Data were expressed as mean \pm standard deviation (mean \pm SD) or n (%) where appropriate. Differences in demographic characteristics and hemodynamic data were evaluated using Student's t test. The chi-square or the Fisher's exact test was used to compare categorical data. A p value less than 0.05 was used as a critical value to assess whether the obtained p values were significant. The analyses were done on a personal computer using SPSS version 14 statistical software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patients' demographic data and ASA physical status categories are shown in table 1. No differences were found between the groups in any of these variables. Duration of anesthesia and surgical intervention, and the time required for LOC were similar between the two groups (Table 2).

During the follow-up period (Figure 1), there were statistically significant differences between the groups with regard to general mean values of MAP ($p < 0.001$). After induction of anesthesia, MAP decreased in both

Table 1. Patients' demographic characteristics (mean \pm SD)

Groups	TCI (n = 20)	DES (n = 20)	P value
Gender (Male/Female)	8/12	13/7	0.095
ASA* physical status I/II (n)	15/5	17/3	0.915
Age (yr)	40 \pm 14	33 \pm 14	0.108
Weight (kg)	69 \pm 13	68 \pm 16	0.718
Height (cm)	166 \pm 6	171 \pm 9	0.091

* ASA: American Society of Anesthesiologists

Table 2. Characteristics of anesthesia management (mean \pm SD)

Groups	TCI (n = 20)	DES (n = 20)	P value
LOC* (min)	1.8 \pm 1.2	2.2 \pm 1.4	0.565
Duration of surgery (min)	107.2 \pm 54.7	153.3 \pm 87.4	0.096
Duration of anesthesia (min)	125.4 \pm 56.6	172.5 \pm 87.6	0.091
Total dose of propofol (mg)	1214.7 \pm 540.5	-	-
Propofol (mg. kg ⁻¹ .h ⁻¹)	8.81 \pm 1.67	-	-
Total dose of remifentanil (μ g)	1033.1 \pm 438.3	1395.7 \pm 5 31.6	0.052
Remifentanil (μ g. kg ⁻¹ .h ⁻¹)	7.48 \pm 1.56	7.69 \pm 1.74	0.052
Propofol Ce (μ g mL ⁻¹)	3.40 \pm 0.29	-	-
ET-Des** (%)	-	4.57 \pm 0.44	-
MAC-Des [†]	-	0.60 \pm 0.06	-

* LOC: Loss of consciousness

** ET-Des: End-tidal concentration of desflurane

[†] MAC-Des: Minimum alveolar concentration value of desflurane**Table 3.** Characteristics of emergence from anesthesia (mean \pm SD)

Groups	TCI (n = 20)	DES (n = 20)	P value
Spontaneous breathing (min)	1.4 \pm 1.4	0.95 \pm 1.4	0.211
Eye opening (min)	5.4 \pm 2.8	5.4 \pm 1.9	0.820
Extubation (min)	5.6 \pm 2.7	5.5 \pm 1.7	0.947
Response to commands (min)	5.9 \pm 2.9	6.5 \pm 2.2	0.512
Orientation (min)	7.1 \pm 2.9	7.8 \pm 2.6	0.529
Patients with PONV* (n)	2	3	0.925
Patients who received analgesic (n)	5	6	0.930

* PONV: Postoperative nausea and vomiting

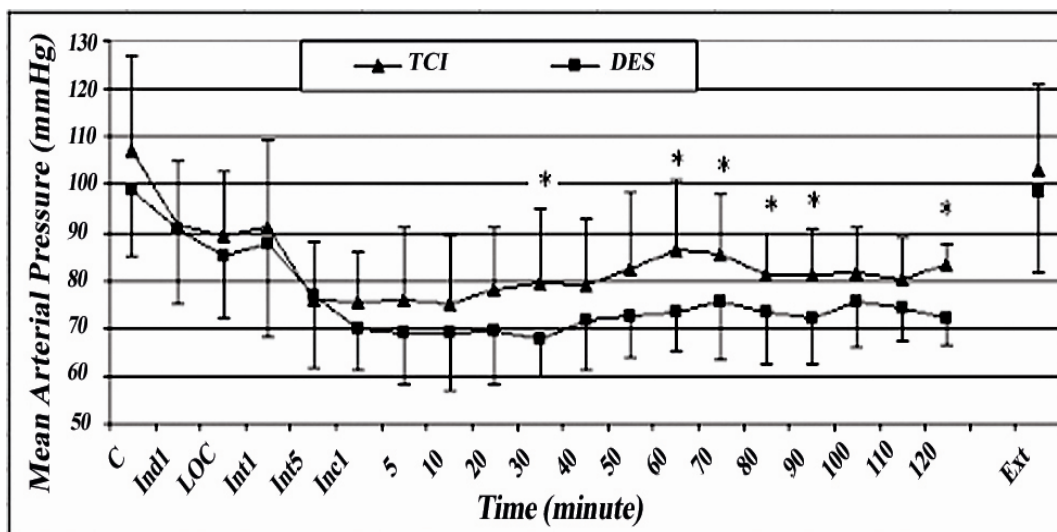


Figure 1. Mean arterial pressure values of TCI and DES groups (mean ± SD)
 C: Control; Ind: Induction; LOC: Loss of consciousness; Int: Intubation; Inc: Incision; Ext: Extubation
 * P < 0.5 versus the DES group

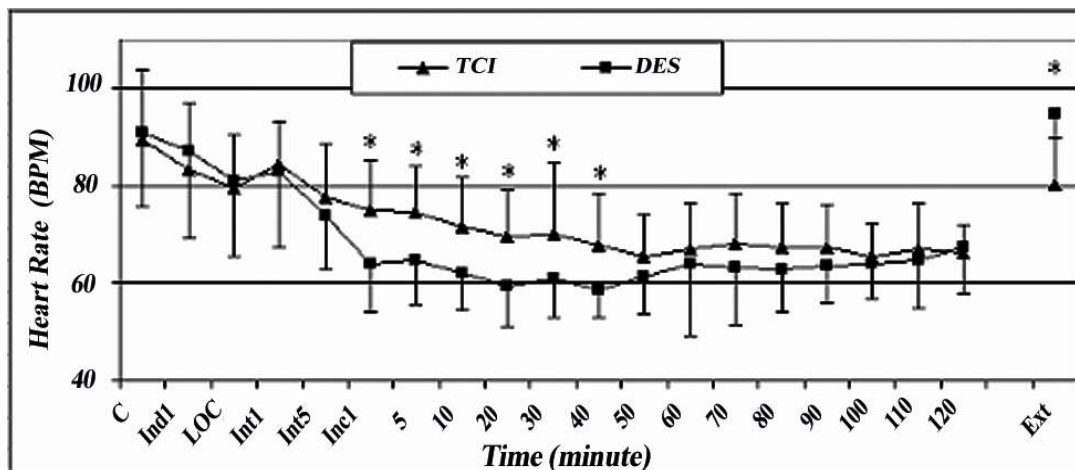


Figure 2. Heart rate values of TCI and DES groups (mean ± SD)
 C: Control; Ind: Induction; LOC: Loss of consciousness; Int: Intubation; Inc: Incision; Ext: Extubation
 * P < 0.5 versus the DES group

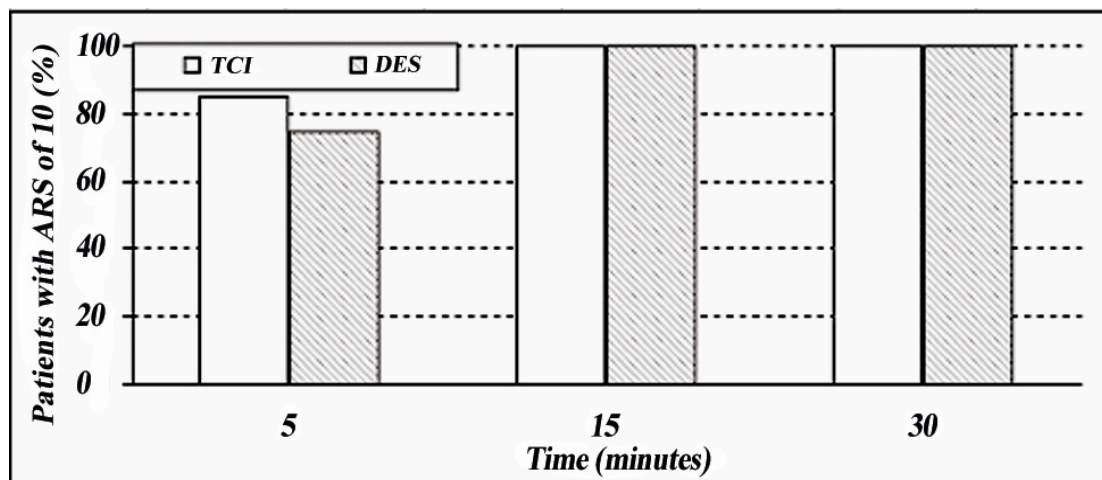


Figure 3. Aldrette Recovery Scoring (ARS) of TCI and DES groups (Figure 3 is not mentioned in the text, remove it or mention it)

groups. In the 1st minute of intubation, there was a slight increase in MAP in both groups; and until the 30th minute, MAP values were between 70-80 mmHg parallel to each other in both groups. The increase in MAP steadily continued and at the 30th, 60th, 70th, 80th, 90th, and 120th minutes, the increase in the TCI group was significantly more than it was in the DES group ($p < 0.05$). At extubation, MAP values reached the baseline values in both groups. In general, MAP values were observed to be within normal limits.

There were statistically significant differences between the groups with regard to general mean values of HR ($p < 0.01$) (Figure 2). Before intubation, HR values decreased insignificantly from the baseline. However, at the 1st minute after the intubation, the values for both groups increased insignificantly. In the following periods, there was still a trend towards lower HR values which were significantly lower 1, 5, 10, 20, 30 and 40 minutes after incision in the DES group than in the TCI group. At extubation, HR values were higher than the baseline values in the DES group whereas HR values were lower than the baseline values in the TCI group, that is, there was a significant difference between the two groups ($p < 0.05$). In general, HR values were observed to be within normal limits.

The total doses of anesthetics given are shown in table 2. There were no significant differences between the groups with regard to remifentanil consumption. The differences in remifentanil consumption occurred due to the difference in the duration of anesthesia. Need for increase or decrease in the remifentanil rate was not required for any of the patients.

The surgical procedures involved in our study were septoplasty, polypectomy, endoscopic sinus surgery, rhinoplasty, nasal reconstructive surgery, or a combination thereof. The incidence and breakdown of these surgical procedures were almost equal.

There was no significant difference between the two groups in the time of emergence from anesthesia (spontaneous ventilation, eye opening, response to commands, extubation and

orientation) (Table 3). In the PACU, there was no significant difference between the two groups in terms of the ARS. During the first 30-minute follow-up in the PACU (Figure 3), 2 patients (10%) in the TCI group, and 3 patients (15%) in the DES group suffered from nausea. None of the patients suffered from vomiting or postoperative shivering. Only 1 patient in each group required antiemetic drugs. In addition, again in this 30-minute period, 5 patients (25%) in TCI group and 6 patients (30%) in DES group stated that they had pain (NRS > 3). However, when all the patients were taken into consideration, mean of NRS value was 3. There was no significant difference between the groups regarding the incidence of PONV and requirement for analgesia. Besides, none of the patients who were visited in the clinic postoperatively stated that they had any problems with regard to pain and anesthetic management. Again, during postoperative visits, no postoperative recall of intra-operative events was observed.

Discussion

Remifentanil may be useful in ENT surgery because of the clinical advantages of remifentanil such as the rapid onset and offset with a context-sensitive half-time of only 3-5 minutes irrespective of the duration of infusion.^{22,23} Furthermore, remifentanil is the most preferred opioid for use in conjunction with propofol based TCI anesthesia. On the other hand, intravenous propofol, currently used for the induction and maintenance of anesthesia, has a favorable pharmacokinetic profile for use with the TCI system.²⁴⁻²⁶ Newer volatile anesthetics such as desflurane have a low blood-gas solubility coefficient, allowing for rapid induction of and rapid recovery from anesthesia similar to propofol.²⁷

One of the problems of many studies is that the depth of anesthesia is determined according to weaker criteria instead of using BIS monitoring for guiding administration of anesthesia. When intravenous and inhalation anesthetics are compared, it is not obvious that the doses used are equianesthetic. To ensure com-

parable depths of anesthesia, the anesthesiologist has to rely on clinical indicators such as blood pressure, heart rate and autonomic signs to titrate the maintenance of anesthetics.^{4,16} Bispectral index was successful in reducing average anesthetic agent consumption and accelerating recovery, and was proved to be useful for measuring the depth of anesthesia.¹¹⁻¹⁵ An index value less than 60 was correlated with LOC and loss of recall in 95% of patients.²¹ The present study was designed to compare the effects of a BIS guided TCI propofol/remifentanil with desflurane/remifentanil anesthesia regimens. In none of the patients in either group did postoperative recall of intraoperative events occur. We believe this was because our study was BIS guided.

The importance of rapid emergence may be quick transfer from the operation room, less work load on the recovery room staff, or even direct transfer from the operation room to phase II recovery, resulting in cost savings. Our patients stayed in hospital for several days postoperatively. The focus of our investigation was the early postanesthetic period where we sought for a fast return to normal recognition and an adequate orientation before discharge from PACU. We found that recovery times were similar with both inhalational and TCI anesthesia in the ENT surgical population.

As mentioned above, to our knowledge, there are no published reports comparing desflurane and propofol TCI anesthesia in combination with remifentanil TCI under BIS guidance. However, when propofol and desflurane anesthesia regimens were compared, various results with regard to recovery profile were obtained. A systematic analysis of the literature comparing postoperative recovery after propofol, isoflurane, desflurane, and sevoflurane based anesthesia in adults demonstrated that early recovery was faster in the desflurane groups.⁵ In another remifentanil based study with desflurane or propofol for laparoscopic cholecystectomy, no differences were demonstrated between the two anesthetic regimens regarding early emergence from anesthesia.⁴ In one of the studies where TCI was used, as the

case is in our study, inhalation anesthesia with desflurane or sevoflurane was compared with propofol delivered by the TCI technique. For this patient group, use of inhalation anesthesia shortened emergence times compared to TCI with propofol with equal perioperative patient conditions.⁶ Again in another study where the TCI technique was used, inhalation anesthesia with desflurane and TCI with propofol anesthetic regimens were compared and no significant difference was observed between the two studies in terms of recovery profiles.⁷

Propofol administered by TCI proved to provide cardiovascular stability and ensure smooth induction and fast stability.^{28,29} In a study where desflurane in combination with etomidate induction was compared to target and manually controlled infusion with propofol anesthetic regimens, desflurane was found to ensure better hemodynamic stability in comparison to manually controlled infusion of propofol and propofol TCI was found to reduce this difference.¹⁰ Again in another remifentanil based study with desflurane or propofol, no major differences were demonstrated between the two anesthetic regimens regarding cardiovascular variables.⁴

In our study, in general, MAP and HR values were observed to be within normal limits and we did not detect any evidence of sympathetic stimulation such as tachycardia or hypertension in either group. We would expect tachycardia and hypertension to occur especially in DES groups as these are among the adverse effects of desflurane.²¹ However, in our study the general mean values of MAP and HR for TCI group were significantly higher than DES group, which is attributed to the combination of desflurane with remifentanil TCI under BIS guidance. In fact, the hemodynamic response to remifentanil appeared to be similar to that to other opioids; that is, a decrease in heart rate and blood pressure may occur.³⁰ Nevertheless, in the present study, the use of TCI technique prevented the occurrence of severe bradycardia and hypotension as well as chest wall rigidity after bolus injections of remifentanil, even during induction of anesthesia.

The primary selection of ENT surgery was of interest in the design of this study because it is associated with a higher risk of PONV. The prevalence of PONV for ENT surgery was around 20% in the desflurane group, consistent with recent reports describing the frequency of PONV in all surgeries to be 20-30%.³¹ Whereas in our study, during the first 30-minute follow-up in the PACU, 10% of patients in the TCI group and 15% of patients in the DES group suffered from nausea. Although our patients underwent ENT surgeries, the PONV rate was found to be lower than it was expected, and this low rate can be explained by monitoring of depth of anesthesia with BIS index during the surgery.

When considered in terms of postoperative pain, in 25% of patients in the TCI group and 30% of patients in the DES group, NRS value was found to be greater than 3 in the PACU. However, when all the patients were taken into consideration, mean of NRS value was 3 in both groups. During postoperative patient visits, none of the patients in either group had any complaints regarding pain and anesthetic management.

This study can be criticized for the fact that the anesthesiologists were aware of the anesthetic drugs being administered, and that the protocol design did not permit a double-blind comparison of the maintenance anesthetic techniques. However, surgical procedures were identical and all of the patients were managed by the same experienced surgeons and anesthesiologists. Accordingly, early recovery was rapid and comparable in both groups. A further improvement in emergence might have been achieved by tapering the amount of re-

mifentanil and of the concomitant hypnotic components down towards the end of surgery instead of continuing with unchanged doses until the end of the wound closure. However, it has been proved that TCI administration of opioids offers better control of emergence, and the application of remifentanil by means of TCI may give a more objective assessment of recovery with its short half life. Another criticism of this study design relates to the lack of investigator blinded in the assessments of early recovery status. However, investigator bias was minimized by using only objective endpoints and by blinding the recovery room nursing staff. The recovery endpoints were evaluated in a blinded fashion by trained individuals who were not involved in the anesthetic administration.

Conclusion

We concluded that BIS guided combinations of remifentanil TCI with either propofol TCI or desflurane anesthetic regimens are both suitable for patients undergoing ENT surgery, providing rapid smooth induction of anesthesia, intraoperative hemodynamic stability and a fast emergence from anesthesia, and with no difference in terms of adverse effects. Additionally, the lower blood pressure in the remifentanil TCI with desflurane anesthetic regimens may be a significant advantage in those procedures where a low blood pressure contributes to the reduction of bleeding.

Acknowledgment

Our study was registered with ClinicalTrials.gov and also an IRCT number was taken (Membership No: 6266, Project No: 1).

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

AM and DC carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. GIK and DTA provided assistance in the design of the study, coordinated and carried out all experiments and participated in manuscript preparation. LK and

YK provided assistance for all experiments. All authors have read and approved the content of the manuscript.

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