Original Article

Effects of the Target-Controlled Infusion of Propofol and Remifentanil on BUN and Creatinine Levels in Patients With Renal Impairment Undergoing Open-Heart Surgeries

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ABSTRACT

Background: The target-controlled infusion (TCI) system controls the plasma concentration of administered drugs, improves hemodynamic stability, prevents the cumulative effect of drugs, provides faster recovery, and perhaps reduces renal complications. We sought to investigate the effects of the TCI method on blood urea nitrogen (BUN) and creatinine (Cr) levels in patients with renal impairment undergoing open-heart surgeries.

Methods: This double-blind clinical trial was performed on 66 patients undergoing cardiac surgeries with preoperative Cr levels of greater than 1.5 mg/dL. The patients were randomly divided into 3 groups. The first group received propofol and remifentanil via the TCI system. The second group received these 3 drugs via the usual dosing (mg/kg) method. The third group received midazolam and fentanyl conventionally (based on the mg/kg method). Postoperative Cr and BUN levels, urine volume, the need for dialysis, and hemodynamic parameters were recorded up to 3 postoperative days. After the exclusion of 10 patients from the study, 56 patients were analyzed.

Results: Postoperative BUN and Cr values were significantly lower in the TCI group than in the other groups (P<0.05) There were no significant differences between the 3 groups concerning hemodynamic status. The total dose of anesthetics was significantly lower in the TCI group than in the propofol-remifentanil group (P<0.05). The incidence of postoperative arrhythmias in the TCI group was significantly lower than that in the other 2 groups (P<0.05).

Conclusions: In our patients with renal dysfunction, the TCI method reduced post-cardiac surgery BUN and Cr levels, the dose of the anesthetics administered, and the incidence of arrhythmias. ***(Iranian Heart Journal 2022; 23(3): 97-107)***

KEYWORDS: Target-controlled infusion, Propofol, Remifentanil, BUN, Creatinine, Cardiac surgery

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The number of heart surgeries has increased due to the increasing trend of heart disease and the increase in facilities required for such operations in most countries. Usually, patients undergoing cardiac surgeries are elderly or have comorbid conditions such as diabetes, hypertension, and kidney disorders. Some patients in situations such as the establishment of a heart and lung bypass pump, in which the tissue absorption of the organs undergoes fluctuations,[1] show greater susceptibility to renal complications due to problems in the renal arteries.[1,2] These patients need lengthier hospitalization after surgical operations and more advanced and expensive medical procedures.[3] Evidence suggests that there should be sufficient awareness of the potential complications for the optimal care of patients undergoing heart surgeries.[4] Acute kidney injury (AKI) is seen sparingly and sometimes seriously after cardiac operations.[5] Indeed, AKI is a rapid decrease in the glomerular filtration rate, which leads to an increase in serum creatinine (Cr), and it is a clinical syndrome that occurs over a period of several hours to several days in association with an increase of 0.3 mg/dL in Cr within 48 hours after surgery or a decrease in urine output to less than 0.5 mg/kg/h in 4 hours.[6] Even slight changes in Cr levels in the postoperative period may reduce patients' chances of survival.[7] It should be noted that about 1% to 3% of such patients need dialysis, and 60% to 70% of the deaths occur among patients on dialysis due to AKI following cardiac surgeries.[8]

The unique characteristics of heart surgeries, including the cardiopulmonary bypass (CPB) pump, the aortic clamp, the number and volume of blood products, high-dose vasopressors, and comorbidities, increase the risk of AKI compared with noncardiac surgeries.[9]

The use of the target-controlled infusion (TCI) method has increased dramatically since 1990. This technique is a computer-controlled instrument and originates from a theoretical approach to achieving the steady-state blood concentration of the drug.[10] To maintain the plasma level of the anesthetic, this device first increases the infusion rate. Thereafter, it decreases the rate and, then, stabilizes it after a short time. Briefly, the infusion begins with the initial bolus of the drug needed to reach the initial target concentration. Next, an infusion is prescribed to replace the drug lost. At plasma steady-state concentrations, drug withdrawal can be compensated with a constant infusion rate. Afterward, the second infusion is prescribed to replace the drug distributed or transferred to the peripheral tissues, and the amount of redistribution is decreased slightly over time, leading to a drop in the gradient between the central and peripheral compartments. This method allows the intravascular anesthetic to reach a target plasma concentration. In addition, in the target organ and plasma, this concentration remains at the desired level and stable during the hemodynamic function and prevents the cumulative effect of drugs, resulting in faster recovery and fewer AKI complications.[11]

Therefore, in the current investigation, we aimed to compare the TCI of remifentanil, propofol, and cisatracurium on blood urea nitrogen (BUN) and Cr levels in patients with renal impairment undergoing open-heart surgeries.

METHODS

The present double-blind clinical trial was performed on candidates for open-heart surgeries with a Cr level of greater than 1.5 mg/dL in a referral cardiac center in Tehran, Iran, between 2016 and 2017. In the design of experiments, consecutive sampling was considered, and patients meeting the study inclusion and exclusion criteria were recruited. The inclusion criteria consisted of a Cr level of greater than 1.5 mg/dL, age between 18 and 70 years, first-time surgeries, and patient satisfaction. The exclusion criteria

were composed of pregnancy, uncontrolled comorbidities (diabetes, hypertension, and hypothyroidism), a CPB time exceeding 120 minutes, complicated and complex heart surgeries, cardiac reoperations, cardiopulmonary resuscitation, severe hemodynamic disorders, high doses of inotropes, and death.

Sample Size

The sample size was calculated to be 66 individuals according to a reference study[12] and a relevant formula. Considering a loss rate of 15%, the final sample size was calculated to be 56.

M1=91.7 m2=100.2 sd1=4.7 sd2=11.8

$$n=\frac{(Z_{(1-\alpha/2)}+Z_{(1-\beta)})^2(sd_1^2+sd_2^2)}{d^2}$$

Procedure

After the provision of informed consent, candidates for open-heart surgeries with a Cr level of greater than 1.5 mg/dL were randomly divided into 3 groups by using online software (www.randomizer.org): TCI (Group I), propofol-remifentanil (Group II), and midazolam-fentanyl (Group III). Totally, 56 patients were analyzed (the CONSORT flow diagram; Fig. 1).

Group I received propofol and remifentanil via the TCI method, Group II received the drugs of the first group in the usual way, and Group III received midazolam, atracurium, and fentanyl. In the TCI group, initial monitoring, including electrocardiography, noninvasive blood pressure monitoring, and procedural oxygen masks, was performed after the patient entered the operating room. Next, intravenous and arterial lines were taken for the patients. Fluid therapy was started at a dose of 7 to 10 mL/kg, and the bispectral index (BIS) monitor was attached to the patients. Sufentanil (1–1.5 mg/kg), propofol (2–2.5 mg/kg), and cisatracurium (0.15–0.2 mg/kg) were used for induction, and the patients were intubated whenever the BIS number reached between 40 and 60.

For maintenance TCI, propofol (1–3 mg/mL) was selected as the target, and remifentanil (2–3 ng/mL) and cisatracurium (40 mg) were then added to the remifentanil syringe.

In Group II, similar to Group I, induction with the same drug and the same dose was performed: propofol (100–150 μg/kg/min) for the maintenance of anesthesia, together with remifentanil (0.1 μg/kg/min) and cisatracurium (1.7 μg /kg/min).

In Group III, like the other 2 groups, midazolam (0.1 mg/kg), atracurium (0.5 mg/kg), and fentanyl (2–20 μg/kg) were used for induction. In the maintenance of this group, midazolam (0.05 mg/kg/h), atracurium (0.7 mg/kg/h), and fentanyl (5 μg /kg/h) were prescribed.

After the operation, a pain pump was prescribed for analgesia. It consisted of a combination of morphine (0.1–0.3 mg/kg daily) and dexmedetomidine (1–3 μg/kg daily). The patients were transferred to the intensive care unit (ICU) after the operation and were monitored for 3 days to evaluate the studied parameters. For the collection of the desired information, a checklist was prepared according to the required variables. Variables were measured before surgery, during surgery, and up to 3 days afterward and were compared between the 3 groups. In this checklist, the patients' demographic characteristics and background (eg, age, sex, and weight), medical history (eg, blood pressure, diabetes, kidney disease, and opium use), and a history of drug use (β-blockers, angiotensin-converting-enzyme inhibitors, calcium blockers, diuretics/vasopressors, analgesics, and corticosteroids) were collected.

During the surgical operation, the heart rate (HR) and the mean arterial pressure (MAP) (on entrance into the operating room, before the start of the pump, immediately after separation from the pump, and before transfer to the ICU), the CPB time, the aortic

cross-clamp time, arrhythmias, the need for intra-aortic balloon pumps, the use of inotropes, the use of vasopressors, and the total dose of anesthetics were recorded.

After the surgical operation, a series of variables were followed for up to 3 days: Cr, BUN, urine volume, the need for dialysis, systolic blood pressure, diastolic blood pressure, MAP, and HR (4 times a day). The cardiac rhythm and the need for inotropes or vasopressors, the time of extubation, the duration of extubation, the appropriate time for ICU discharge, and the duration of ICU admission were recorded.

All the patients were blinded to the type of anesthesia.

Statistical Analysis

The results of the statistical analyses were reported as percentages for qualitative variables. The χ^2 and Fisher exact tests were used to examine the relationships between the qualitative variables. For some nonparametric quantitative variables, the Kruskal–Wallis test was utilized. The obtained data were analyzed using the SPSS statistical software, version 23, and a *P* value of 0.05 or less was considered statistically significant.

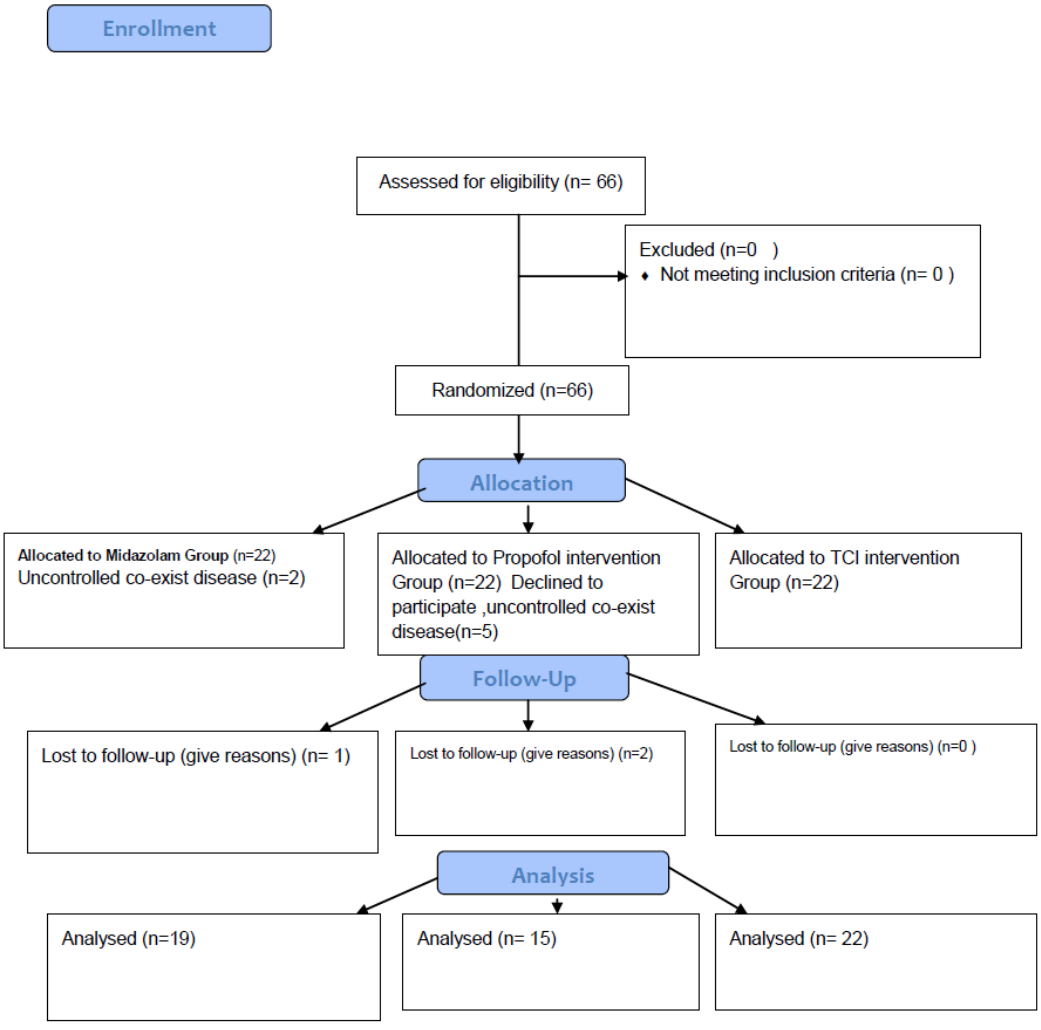

Figure 1: The image depicts the study flow diagram.

Ethical Considerations

Written informed consent was obtained from all the subjects. All patient information remained confidential. The ethical principles of the Helsinki Declaration were observed. No additional costs were imposed on the patients. Before entering the study, all the patients were given full explanations regarding treatment methods, medications, and possible side effects. The study was carried out after approval by the Research Council of the Medical School and receiving the code of ethics (IR.IUMS.FMD.REC.1399.130) and a letter of introduction.

RESULTS

Of the 56 patients included in the study, 22 patients were included in the TCI group, 15 patients in the propofol-remifentanil group, and 19 patients in the midazolam-fentanyl group.

There were 39 male patients: 16 patients (41%) in the TCI group, 11 patients (28.1%) in the propofol-remifentanil group, and 12 patients (30.72%) in the midazolam-fentanyl group. There was no statistically significant difference between the 3 groups in terms of sex (P=0.751). The mean age was 65 years in the TCI group, 64 years in the propofol-remifentanil group, and 59 years in the midazolam-fentanyl group. A statistically significant age difference was found between the 3 groups (P=0.038).

The history of comorbidities is listed in Table 1. In the midazolam-fentanyl group, blood pressure, kidney disease, and addiction had the highest frequencies, followed by diabetes in the TCI group and hypothyroidism in the propofol-remifentanil group. No statistically significant differences were found between the studied groups in this regard (P>0.05).

Table 2 presents the renal function status of the patients before surgery and up to 3 days afterward. There were no statistically significant differences in urine volume and the need for dialysis between the 3 groups during the 3-day period (P>0.05). The comparison of the Cr values of the patients before and after surgery in the ICU is shown in Figure 2. There was no significant difference before the operation between the 3 groups (P=0.591). On the first day of ICU admission, the amount of Cr in the TCI group was lower than that in the other 2 groups, although no significant difference was seen (P=0.066). There was a significant difference between the 3 groups on the second day (P=0.033) and the third day (P=0.025) regarding the Cr level. A comparison of pre-and postoperative BUN values in the ICU is shown in Figure 3. There was no significant difference in preoperative BUN between the 3 groups (P=0.191), but significant differences were found between the 3 groups on the first day (P=0.046), the second day (P=0.028), and the third day (P=0.027) after ICU admission.

Table 3 demonstrates the hemodynamic status of the patients during surgery, at the beginning of entering the operating room, before the start of the pump, immediately after separation from the pump, and before transfer to the ICU in all 3 groups. The frequency of rhythm disturbances before and after surgery was examined in all 3 groups. Two patients (9.1%) in the TCI group had preoperative rhythm disorders, followed by 4 patients (26.7%) in the propofol-remifentanil group and 3 patients (15.8%) in the midazolam-fentanyl group, with the difference between the groups failing to constitute statistical significance (P=0.36). Postoperative arrhythmias were reported in 1 patient (4.5%) in the TCI group, 7 patients (46.7%) in the propofol-remifentanil group, and 3 patients (15.8%) in the midazolam-fentanyl group; the difference between the 3 groups was statistically significant (P=0.006). The results showed that the TCI group had the fewest rhythm disturbances.

Table 1: Frequency distribution of the history of comorbidities

Variables	Target-Controlled Infusion	Propofol-Remifentanil	Midazolam-Fentanyl	*P* value
Hypertension	16 (77.3%)	0	18 (94.7%)	0.091
Diabetes mellitus	13 (59.1%)	7 (46.7%)	6 (31.6%)	0.212
Renal disease	13 (59.1%)	7 (46.7%)	14 (73.7%)	0.272
Hyperthyroidism	1 (4.5%)	3 (20%)	0	0.085
Addiction	4 (18.2%)	2 (13.3%)	5 (26.3%)	0.624

Table 2: Comparison of urine volume and the need for postoperative dialysis in the intensive care unit

Variables	Target-Controlled Infusion	Propofol-Remifentanil	Midazolam-Fentanyl	*P* value
First-day urine volume (mL)	2500 (2125-3275)	2200 (400-2600)	2400 (1300-3000)	0.109
Second-day urine volume (mL)	2850 (2150-3525)	2300 (150-3000)	2100 (1520-3200)	0.065
Third-day urine volume (mL)	2800 (1975-3275)	1700 (230-2500)	2400 (1700-3200)	0.080
Requiring preoperative dialysis	0	2 (13.3%)	5 (26.3%)	0.021
Requiring postoperative dialysis on the first day	0	2 (13.3%)	1 (5.3%)	0.179
Requiring postoperative dialysis on the second day	1 (4.5%)	1 (6.7%)	4 (21.1%)	0.196
Requiring postoperative dialysis on the third day	0	2 (13.3%)	3 (15.8%)	0.11

Table 3: Comparison of the mean values of the patients' hemodynamic variables during surgery

Variables	Target-Controlled Infusion	Propofol-Remifentanil	Midazolam-Fentanyl	*P* value
HR (bpm)	70 (60-85)	70 (65-80)	75 (68-81)	0.619
SBP (mm Hg)	132.5 (115-152.5)	130 (120-140)	130 (110-140)	0.697
DBP (mm Hg)	80 (65-86.25)	75 (70-90)	70 (68-81)	0.217
MAP (mm Hg)	70(65-76/250)	70(60-80)	70(65-70)	0.685

HR, Heart rate; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure

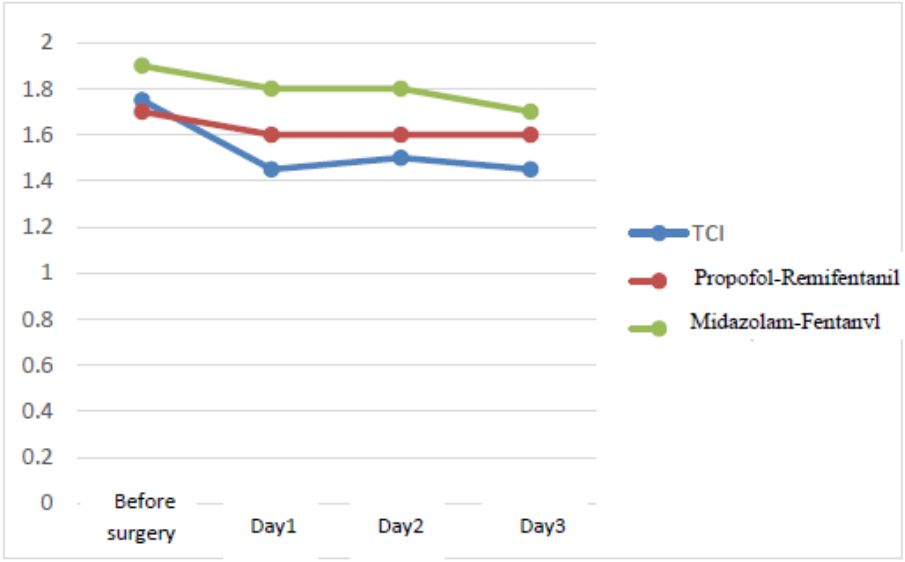

Figure 2: The figure presents a comparison of the creatinine (Cr) values of the patients before and after surgery in the intensive care unit.

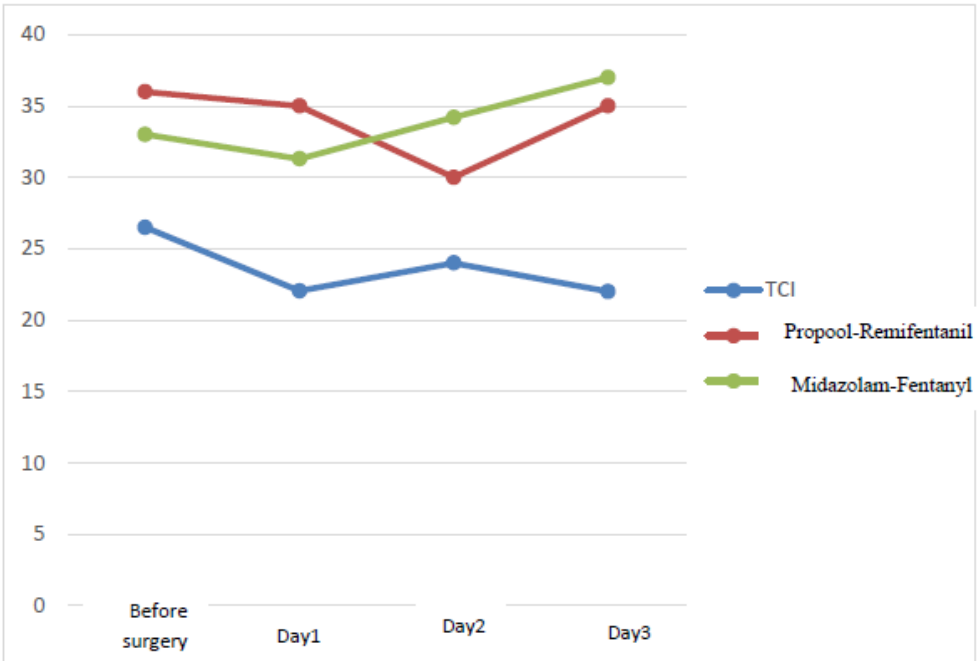

Figure 3: The figure presents a comparison of the blood urea nitrogen (BUN) values of the patients before and after surgery in the intensive care unit.

A comparison of the time of patient awaking, feasibility for extubation, and the real extubation time, as well as a comparison of the ICU length of stay, was done between all 3 groups. The time of feasibility for extubation was 10 hours in the TCI and propofol-remifentanil groups and 12 hours in the midazolam-fentanyl group (P=0982). The real intubation time was 11 hours in the TCI group, followed by 12 hours in the propofol-remifentanil group and 14 hours in the midazolam-fentanyl group (P=0.315). The ICU length of stay was not statistically significantly different between the groups (P>0.05).

Table 4 lists the frequencies of milrinone and epinephrine intake in the operating room and the ICU. The TCI group did not receive milrinone in the operating room, and there was a significant difference between the 3 groups (P=0.011). In the ICU, there was no significant difference between the 3 groups regarding inotrope administration (P>0.05). The hemodynamic status of the patients in all 3 groups during the 3-day period of ICU stay was compared (Table 5), and there were no significant differences between the 3 studied groups (P>0.05).

A comparison of the total doses of anesthetic drugs was performed between the TCI and propofol-remifentanil groups. The total dose of propofol was 885 mg in the TCI group and 1620 mg in the propofol-remifentanil group. Furthermore, the dose of cisatracurium was 18 mg in the TCI group and 27 mg in the propofol-remifentanil group. In addition, the total dose of remifentanil was 1.5 mg in the TCI group and 1.7 mg in the propofol-remifentanil group. There were statistically significant differences between the 2 groups regarding the total doses of the abovementioned agents (P=0.0001).

Table 4: Frequencies of the use of vasopressors and inotropes (milrinone and epinephrine) used during and after surgery

Variables	Target-Controlled Infusion	Propofol-Remifentanil	Midazolam-Fentanyl	*P* value
Milrinone during surgery	0	5 (33.3%)	3 (15.8%)	0.011
Milrinone after surgery	0	2 (13.3%)	3 (15.8%)	0.164
Epinephrine during surgery	10 (45.5%)	8 (53.3%)	8 (42.1%)	0.803
Postoperative epinephrine	5 (22.7%)	6 (40%)	6 (31.6%)	0.528

Table 5: Comparison of the mean values of the patients' hemodynamic variables (HR-MAP) in the ICU between all 3 groups

Variables	Target-Controlled Infusion	Propofol-Remifentanil	Midazolam-Fentanyl	*P* value
First-day MAP (mm Hg)	81.5 (74.25-90.75)	82(65-92)	69(65-83)	0.055
Second-day MAP (mm Hg)	84.5 (75.75-93)	85(80-96)	83(72-94)	0.885
Third-day MAP (mm Hg)	83 (75-96.25)	82(73-90)	83(79-90)	0.785
HR on the first day	85 (70-90)	85(80-95)	85(78-95)	0.549
HR on the second day	80 (74.75-91)	90(82-100)	87(73-95)	0.265
HR on the third day	80 (70-90)	85(74-90)	85(71-90)	0.422

HR; Heart rate; MAP, Mean arterial pressure

DISCUSSION

The TCI system aims to control the plasma concentration of anesthetic drugs to improve hemodynamic stability, prevent the cumulative effect of drugs, and provide faster recovery. Additionally, the TCI system could be effective in reducing renal complications.[13]

In the present study, we evaluated the effects of the TCI method on the levels of BUN and Cr in patients with renal impairment undergoing open-heart surgeries. Our results showed that the total dose of anesthetics via the TCI method was significantly lower than that via conventional anesthesia infusion methods (P<0.0001).

In a study by De Castro et al,[14] 46 patients scheduled for carotid surgery were enrolled to compare intra- and postoperative hemodynamics, the need for remifentanil during anesthesia, and the need for postoperative morphine. Their results showed that the TCI group had a lower requirement for remifentanil (P<0.001), but there was no difference in the need for propofol between the 2 groups. The maintenance dose and the total remifentanil requirement in the TCI group were lower than those in the regional intravenous anesthesia group. Their results are consistent with our study in terms of the total dose of anesthetics (P<0.0001).

In the present study, there were no significant differences concerning MAP and HR between the 3 groups (P>0.05). According to a study conducted by Tantry et al[15] (2013), 34 patients were candidates for shoulder arthroscopy. In 1 group, propofol was used for TCI maintenance, and sevoflurane was used in the second group. In the first group, the target plasma concentration of propofol was 3 μg/mL, and sevoflurane with a minimum alveolar concentration of 1.2% to 1.5% was used in the second group. Their results showed that the use of TCI propofol significantly reduced systolic blood pressure and MAP compared with the sevoflurane group. Therefore, it seems that TCI propofol was preferable to sevoflurane in patients undergoing shoulder arthroscopy. This finding does not chime in with the results of the present study. The type of surgery in the

investigation by Tantry and colleagues was shoulder arthroscopy, which entails less bleeding. Therefore, a total dose of 3 μg/mL was chosen for propofol in their study, while in our present study, the focus was on open-heart surgeries, in which hemodynamics should be stable during surgery according to the age and underlying diseases of patients. High blood pressure is detrimental to patients. We detected no reduction in MAP and HR in the present study, which may explain the lack of a significant difference between the 3 groups.

The main objective of the present study was to investigate the difference in postoperative BUN and Cr between the 3 groups. Our findings showed that postoperative BUN and Cr were lower in the TCI group than in the other 2 groups, with a statistically significant difference between the groups.

In a study conducted by Ji Wook Kim et al[16] (2013), renal and hepatic tests were compared between 2 groups of patients scheduled for an elective thyroidectomy who received sevoflurane-remifentanil and TCI propofol and remifentanil. Changes in renal and hepatic tests after thyroidectomy were not significantly different between the 2 groups, while postoperative BUN and Cr were significantly lower in the TCI group than in the other 2 groups ($P<0.05$). In this respect, their findings are not consistent with ours. Due to the short duration of thyroidectomy and given the American Society of Anesthesiologists (ASA) Physical Status Classification System classes I and II, it can be expected that Cr does not increase in either group. Although there was an increase in BUN, it was within the normal range, and no significant difference was seen between the 2 groups, which could explain the difference between their results and ours.

Another goal of our study was to investigate the difference between the duration of intubation in the ICU. In this regard, we found no significant difference between the 3 groups ($P>0.05$).

In a prospective comparative study, El-Attar et al[17] (2014) compared the effect of TCI of propofol-fentanyl and desflurane in patients undergoing liver resection. Fifty adult cirrhotic patients were randomly divided into 2 groups. In the TCI group, fentanyl (3 μg/kg) was injected for 30 seconds before anesthesia, followed by an infusion (2 μg/kg/h) for 30 minutes, an infusion (1.5 μg/kg/h) from minute 31 to minute 150, and an infusion (1 μg/kg/h) until 30 minutes before the end of surgery. ICU admission and hospital stay were similar in both groups. In the TCI group, the extubation time was longer and economically more cost-effective. The authors concluded that desflurane was a better choice than TCI propofol-fentanyl in cirrhotic patients undergoing major liver resection surgery. Regarding the duration of the extubation of patients, the finding of their study is not in line with the present study, which might be the reason for the high dose of propofol in the aforementioned study in comparison with our study. This reason could be the cause of longer extubation among the patients in the TCI group in that study.

Another aim of the current study was to evaluate the duration of ICU admission. In this regard, our results yielded no significant difference between the 3 groups ($P>0.05$), which is concordant with the results of a study by El-Attar et al[17] (2014).

We also sought to determine the difference in the use of inotropes and vasopressors between the 3 groups. Our results demonstrated a significant difference in the use of milrinone during surgery between the 3 groups ($P=0.011$).

In a study by Lehman et al,[18] aimed at comparing hemodynamics, the time to extubation, and the costs of TCI, the TCI method with manually controlled infusion (MCI) of propofol was performed in high-

risk cardiac surgery patients. Propofol was applied as TCI (plasma target concentration: 2–3 μg/mL; n=10) or MCI (2.5–3.5 mg/kg/h; n=10). Hemodynamics were measured at 6 data points. No significant hemodynamic differences were found between the 2 groups. Further, dobutamine was required significantly more to maintain a cardiac index of greater than 2 L/min/m^2 in the TCI group than in the MCI group. In terms of the intraoperative use of inotropic drugs, that study is not consistent with the present study. Perhaps one of the reasons is the use of a lower dose of propofol in our study because the target dose of propofol in the present study was 1 to 2 μg/mL, which is sometimes less regarding the BIS number.[19,20] Additionally, all the patients in this study group had decreased left ventricular function, which can increase the need for inotropes. On the other hand, the number of patients in the TCI group of the mentioned study (10 patients) was less than that of our study (22 patients). These reasons may explain the difference between the results of the 2 studies.

CONCLUSIONS

It seems that the use of the TCI method in patients with renal dysfunction blunts BUN and Cr increase after cardiac surgeries. Moreover, the TCI method might reduce the total dose of anesthetics and the occurrence rate of postoperative arrhythmias.

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