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CLINICAL STUDY

A comparison of the effects of ketamine and remifentanyl on renal functions in coronary artery bypass graft surgery

Aslı Demir¹, Fatma Meric Yılmaz², Cavit Ceylan³, Omer Gokhan Doluoglu⁴, Perihan Uçar¹, Cevdet Züngün², Cigdem Yildirim Guclu⁵, Utku Ünal⁶, Umit Karadeniz¹, Eren Günertem⁶, Gokhan Lafci⁶, Kerim Çağlı⁶, and Ayşegül Özgök¹

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Abstract

We have investigated the effects of ketamine-based and remifentanyl-based anesthetic protocol on perioperative serum cystatin-C levels, and creatinine and/or cystatin-C-based eGFR equations in terms of acute kidney injury in coronary artery bypass graft (CABG) surgery. Using a simple randomization method (coin tossing), patients were divided into the two groups and not-blinded to the anesthetist. Remifentanyl–midazolam–propofol or ketamine–midazolam–propofol-based anesthetic regimen was chosen. Different eGFR formulas using creatinine (MDRD, CKD-EPI, Cockcroft Gault); cystatin-C (eGFR1, eGFR2) or a combination of creatinine and cystatin-C (eGFR 3) were used to calculate estimated glomerular filtration rates (eGFRs). High-sensitive troponin T was used to determine if ketamine use in coronary surgery contributed to myocardial cell damage. Thirty-seven patients were included in the study (remifentanyl group = 19, ketamine group = 18). Urea, creatinine, cystatin-C levels were comparable between the groups in all the measurement times and also postoperative day 2 samples showed statistically higher results compared to baseline ($p < 0.001$). Effects of ketamine and remifentanyl on renal functions were found similar. Creatinine and cystatin-C-based eGFR equations resulted similar in our study. Reversible stage 1 acute kidney injury (AKI) was observed on postoperative day 2 in seven patients from the remifentanyl group and six patients from the ketamine group. Hs-troponin T was found to be higher in postoperative day 1 samples; there were no significant difference between the groups. Our results indicated that patients who have normal renal functions undergoing on-pump coronary bypass surgery, effects of ketamine and remifentanyl on renal functions in terms of AKI were found to be similar.

Keywords

Acute kidney injury, anesthetics, coronary artery bypass, ketamine, remifentanyl

History

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Introduction

Acute kidney injury (AKI) occurring following on-pump heart surgery is a condition elevating multifactorial morbidity and mortality. AKI causes an increase in length of stay in both intensive care and hospital.¹ Several factors, such as low arterial blood pressure, toxins, metabolic factors, hypoxia-reoxygenation, neurohumoral activation and systemic inflammation play a role in AKI patho-physiology.² Exogenous factors inducing this pathology include cardiopulmonary bypass (CPB), hypothermia, transfusion, cross-clamp and CPB duration, complicated and combined surgeries, hemodilution, thromboemboli and artificial and medical heart supports. Among endogenous factors are advanced age, female gender, chronic obstructive pulmonary disease,

diabetes mellitus, peripheral vascular disease, poor ventricle, emergent surgery and the individual's basal kidney functions, antioxidant capacity and response to inflammation.^{3,4}

Serum cystatin-C is a valuable predictive biomarker of AKI following CPB.^{5,6} It was claimed that the use of cystatin-C shortens time to diagnosis of AKI by 1–2 days in patients in critical conditions.⁷ It was shown that ketamine reduces the systemic inflammatory response induced by CPB and it has anti-inflammatory properties.^{8–10} Although the use of ketamine is considered as disadvantageous in cardiac surgery because it causes an increase in blood pressure, ketamine–midazolam–propofol combination balances the blood pressure. Hypotension that may occur with opioid combinations does not develop with ketamine, and thus organ perfusions may be protected without vasoactive medicine.

In this study, we investigated the possible positive effects of ketamine (used as a sole analgesic in patients undergoing elective coronary surgery), which was shown to have positive impacts on the immune system, and on renal functions. Our primary hypothesis is that ketamine decreases acute kidney

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dysfunction and injury, as measured by postoperative cystatin-C levels undergoing coronary surgery. We also hypothesized that whether a ketamine-based regimen puts coronary patients at extra risk of myocardial injury, as measured by high-sensitive cardiac troponin levels.

Materials and methods

This study was approved by the Ethics Committee of Hospital (paperwork date/number: April 9th 2013/3979), had a clinical trial number of NCT02113150 and all patients were informed and gave written consent. Forty patients scheduled for elective CABG with cardiopulmonary bypass were enrolled in the study. We excluded patients undergoing emergency operation, combined operation, off-pump surgery, repeat surgery or valve surgery, patients presenting with chronic kidney disease or renal impairment, patients younger than 18 years old and neurological and/or psychiatric disturbances, patients who underwent angiography more than a week shortly before. Patients were scored using EuroSCORE II (Papworth Hospital, Cambridge, UK). Preoperative medications were continued until the morning of the operation. Standard premedication regimen was used in all patients (Figure 1). Using a simple randomization method (coin tossing), patients were divided into the two groups and not-blinded to the anesthetist. Remifentanyl–midazolam–propofol or ketamine–midazolam–propofol-based anesthetic regimen was chosen (Figure 1) for induction and maintenance. All patients in this study received propofol and midazolam in order to prevent ketamine-induced hallucinations. Rocuronium was used as a muscle relaxant. During the operation (except for CPB period) systolic arterial pressure and heart rate were maintained within $\pm 20\%$ of baseline. Hemodynamic changes occurred during anesthesia (tachycardia = pulse > 100 beat/min, hypertension = systolic arterial pressure (SAP) > 160 mmHg, hypotension = SAP < 100 mmHg) were corrected using anesthetic medicine, cardiovascular medicine or fluids.

Monitoring included 5-lead electrocardiography (ECG), pulse oximetry, invasive artery and central venous access, urinary catheter, temperature probe, capnography and bispectral index (BIS). Routine surgical techniques and cardioprotection strategies were utilized in all patients. Patients had median sternotomy with harvesting saphenous vein and internal mammary artery. CPB was performed in the patients. Following the surgery, the patients were admitted to the intensive care unit (ICU) intubated, and weaned once they achieved proper breathing and hemodynamics. Blood samples were obtained before the induction of anesthesia (baseline), at the end of the operation and morning of postoperative days 1, 2 and 4.

Biochemistry analysis

All samples were centrifuged for 10 min at 1300 g; after the completion of clotting, they were stored at -20°C until analysis. All of the analyses were performed on the same day. Cystatin-C levels were determined in a Roche Modular P analyzer (Roche Diagnostics, Germany) and high sensitive troponin t levels were analyzed using a Cobas E601 analyzer (Roche, Germany) with original reagents. Different eGFR formulas using creatinine (Modification of Diet in Renal

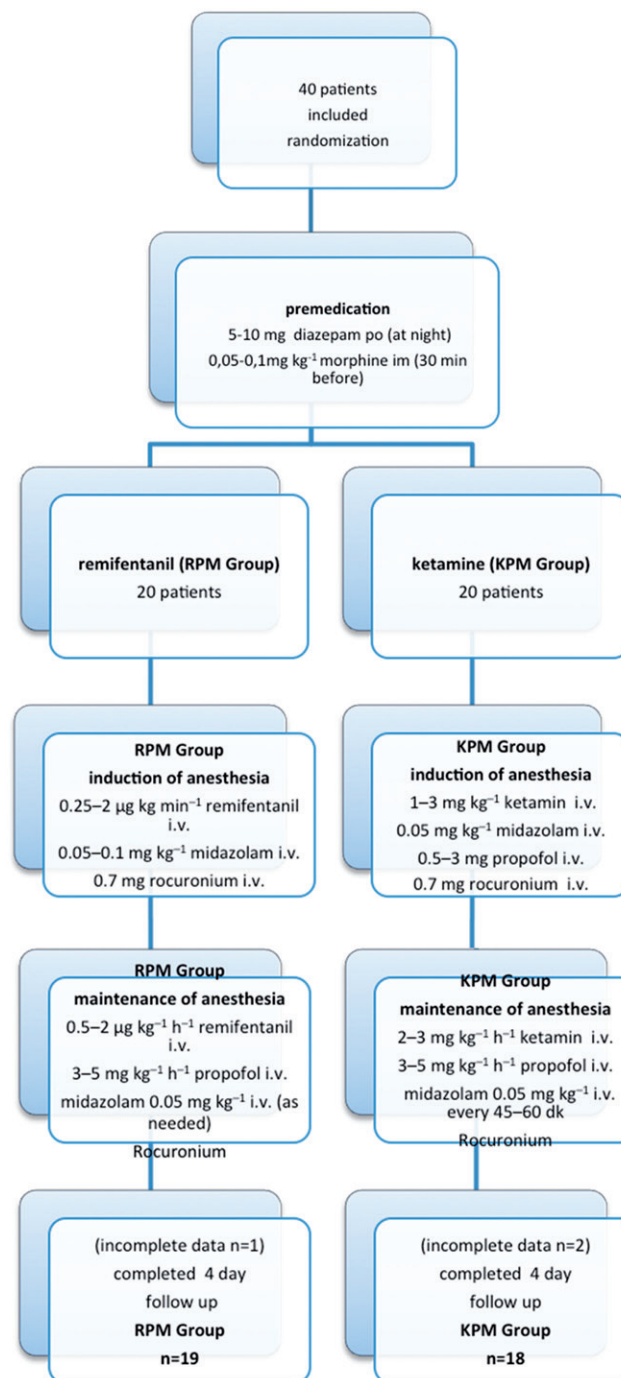


Figure 1. Anesthetic regimens and management.

Disease [MDRD], The Chronic Kidney Disease Epidemiology [CKD-EPI, Cockcroft Gault]; cystatin-C (eGFR1, eGFR2) or a combination of creatinine and cystatin-C (eGFR 3) were used to calculate estimated glomerular filtration rates (eGFRs). Gold standard procedures for measurement of GFR (inulin, iothexol, ^{51}Cr -EDTA, $^{99\text{m}}\text{Tc}$ -DTPA and ^{125}I -iothalamate clearance) are time-consuming, have side effects for patient or expensive.^{11,12} Estimated GFR (eGFR) formulas have been developed and used in more than 80% of clinical laboratories in the United States because of the aforementioned problems.¹³ The most common formulas used in the calculation of eGFR

include MDRD and recently CKD-EPI equations.^{14,15} These equations were developed to determine eGFR based on not only serum creatinine but also demographic variables, such as age, gender and race.¹⁶ It has been suggested that cystatin-C, which is used in eGFR estimations, gives more reliable results when used alone or with serum creatinine and other demographic variables.¹⁷ Calculation of GFR by serum creatinine alone is affected by low- or high-muscle mass, diet and medications which have influence on tubular secretion. In vast majority of the studies with cystatin-C, it was reported that cystatin-C is a better marker for demonstrating GFR and its efficiency increases especially when used with keratinize.¹⁷ Furthermore, cystatin-C responds more quickly to the decrease in GFR; cystatin-C starts to increase when GFR falls below 80 mL/min, but creatinine starts to increase when GFR falls below 40 mL/min.¹⁸ For these reasons, cystatin-C is suggested to be more useful for demonstrating mild to moderate renal function disorders.¹⁹ High-sensitive troponin T was used to determine if ketamine use in coronary surgery contributed to myocardial cell damage.

Statistical analysis

Data were analyzed using SPSS for Win 15 (SPSS/IBM, Chicago, IL). Descriptive statistics were presented as mean $\pm$ SD for normally distributed variables, median (min–max) for abnormally distributed variables and the number of case and percentage (%) for nominal variables. When it is normally distributed, the significance of the mean differences between times and groups was achieved by variance analysis test with repeated measurements. The significance of the median difference and significance of differences between in-group times were analyzed using Friedman's test with Bonferroni correction. In case of a difference, multi-comparisons between times were evaluated using proper *post-hoc* tests. Intergroup means differences were evaluated using independent *t*-test, and the differences in medians were evaluated using Mann–Whitney test. Nominal variables were evaluated using Pearson's Chi-square and Fisher's exact tests. $p < 0.05$ was considered statistically significant. Reference values for cystatin-C have shown to be between 0.52 and 0.98 mg/L with a standard deviation of 0.19 mg/L.²⁰ Elevated serum cystatin-C was defined as ≥ 1.09 mg/L at the study of Muntner et al.²¹ At least one SD elevation was assumed to be different among groups with regard to that paper.²¹ *Post-hoc* power analysis revealed that this study has a power of 84% with these values. Power analysis was performed using the G*Power software (G*Power Version 3.1.5, Kiel, Germany).

Results

A total of 37 patients were studied (remifentanyl group = 19, ketamine group = 18). Three patients were excluded due to missing data. Patient characteristics, preoperative medication, EuroSCORE II and cardiac profile data were similar between the groups (Table 1).

During the intraoperative period, cross-clamp time, CPB time, the need for transfusion and 28-day mortality rates were found similar between groups (Table 2). During anesthesia period, SAP and heart rate (HR) were found to be higher in the ketamine group, which was not statistically significant.

Table 1. Patient characteristics, preoperative medication, euroscore II and cardiac profile data.

Parameter	RPM group (n = 19)	KPM group (n = 18)	p Values
Age (year) (mean $\pm$ SD)	61 $\pm$ 6.9	59 $\pm$ 8.7	0.329
Height (cm) (mean $\pm$ SD)	164 $\pm$ 8.3	166 $\pm$ 8.8	0.587
Weight (kg) (mean $\pm$ SD)	76 $\pm$ 11.5	79 $\pm$ 12.6	0.335
BMI (kgm ⁻²) (median, min–max)	28.1 (22–35)	28.7 (22–36)	0.455
Gender (M/F)	11/8	15/3	0.091
EF (%) (median)	55	55	0.413
EuroScore II (median, min–max)	0.98 (0.6–2.2)	0.75 (0.5–2.2)	0.06
DM (n)	8	6	0.582
HT (n)	12	12	0.07
COPD (n)	3	6	0.486
B-blocker (n)	19	18	0.752
ACE inhibitors (n)	14	10	0.138
Ca blockers (n)	2	2	1
Nitrates (n)	16	18	0.693
Diuretics (n)	3	3	0.98
Statins (n)	12	11	0.898
ASAII/III (n)	8/11	10/8	0.516

Notes: RPM: remifentanyl–propofol–midazolam; KPM: ketamine–propofol–midazolam, BMI: body mass index; EF: ejection fraction; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease.

Table 2. Intraoperative data, 28 day mortality.

Parameter	RPM group (n = 19)	KPM group (n = 18)	p Values
AoX duration (min) (median)	54 (13–80)	51 (31–97)	0.641
CPB duration (min) (median)	97 (70–124)	94 (74–115)	0.711
Anesthesia duration (h) (median)	3.5 (2–5)	3 (3–5)	0.258
RBC (units) (median)	1 (0–2)	1 (0–2)	0.620
FFP (patients of given 1 U)	6	6	0.909
Vessels (n) (median)	3 (1–4)	3 (1–5)	0.960
28 day mortality (n)	0	0	–

Notes: RPM: remifentanyl–propofol–midazolam; KPM: ketamine–propofol–midazolam, AoX: aortic cross clamp; CPB: cardiopulmonary bypass; RBC: red blood cell; FFP: fresh frozen plasma.

Urea (Figure 2), creatinine (Figure 3), and cystatin-C (Figure 4) levels were comparable between the groups in all of the timings and also postoperative day 2 samples showed statistically (except urea) higher results compared to baseline ($p < 0.001$). In the remifentanyl group, baseline urea levels were 33 ± 13 mgdL⁻¹; postoperative second day levels were 44 ± 21 mgdL⁻¹; in the ketamine group, baseline urea levels were 31 ± 17 mgdL⁻¹; postoperative second day levels were 42 ± 21 mgdL⁻¹. In the remifentanyl group, baseline creatinine levels were 0.82 ± 0.18 mgdL⁻¹; postoperative second day creatinine levels were 1.06 ± 0.33 mgdL⁻¹; in the ketamine group baseline creatinine levels were 0.97 ± 0.36 mgdL⁻¹; postoperative second day creatinine levels were 1.20 ± 0.55 mgdL⁻¹. In the remifentanyl group, baseline cystatin-C levels were 0.90 ± 0.13 mgL⁻¹; postoperative second day cystatin-C levels were 1.12 ± 0.22 mgL⁻¹; in the ketamine group, baseline cystatin-C levels were 1.05 ± 0.26 mgL⁻¹; postoperative second day cystatin-C levels were 1.27 ± 0.36 mgdL⁻¹.

Figure 2. Urea levels (mg dL^{-1}) are presented as box plots for each group and time point. Note: For remifentanyl group: urea 2–4 $p < 0.01$, urea 3–4 $p < 0.05$, urea 4–5 $p < 0.001$. For group KPM: urea 2–4 $p < 0.05$, urea 3–4 $p < 0.05$.

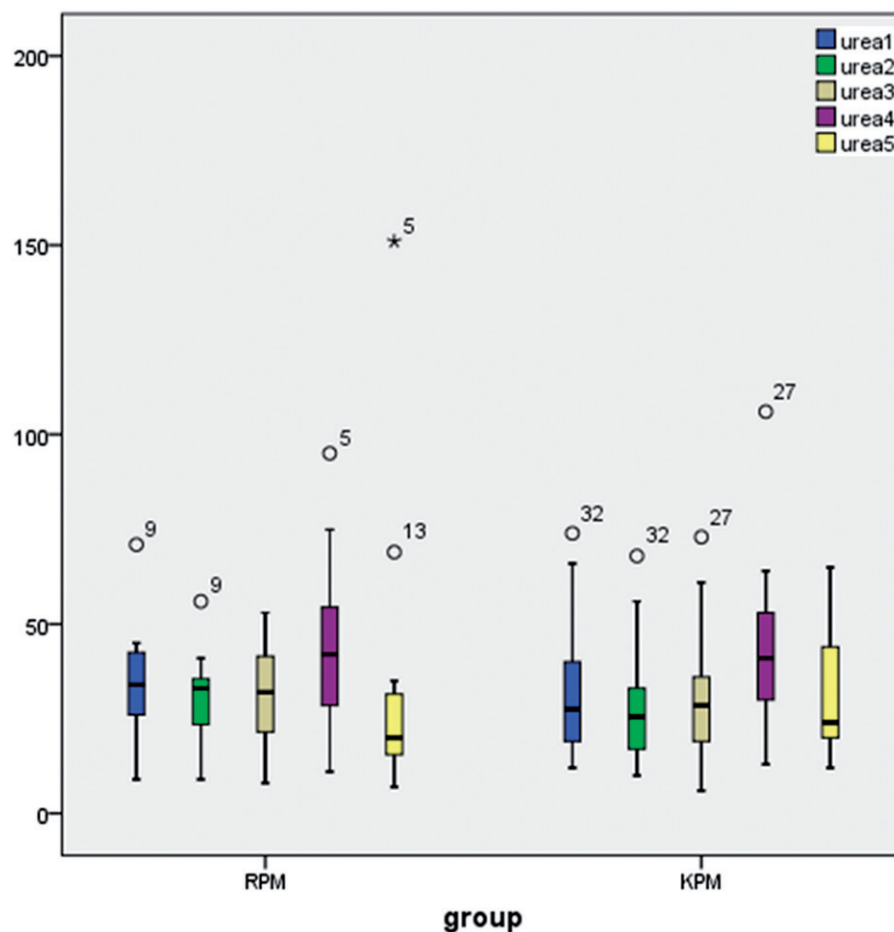


Figure 3. Creatinine levels (mg dL^{-1}) are presented as box plots for each group and time point. Note: Both for groups Creatinine 1–4 $p < 0.05$, Creatinine 2–4 $p < 0.001$.

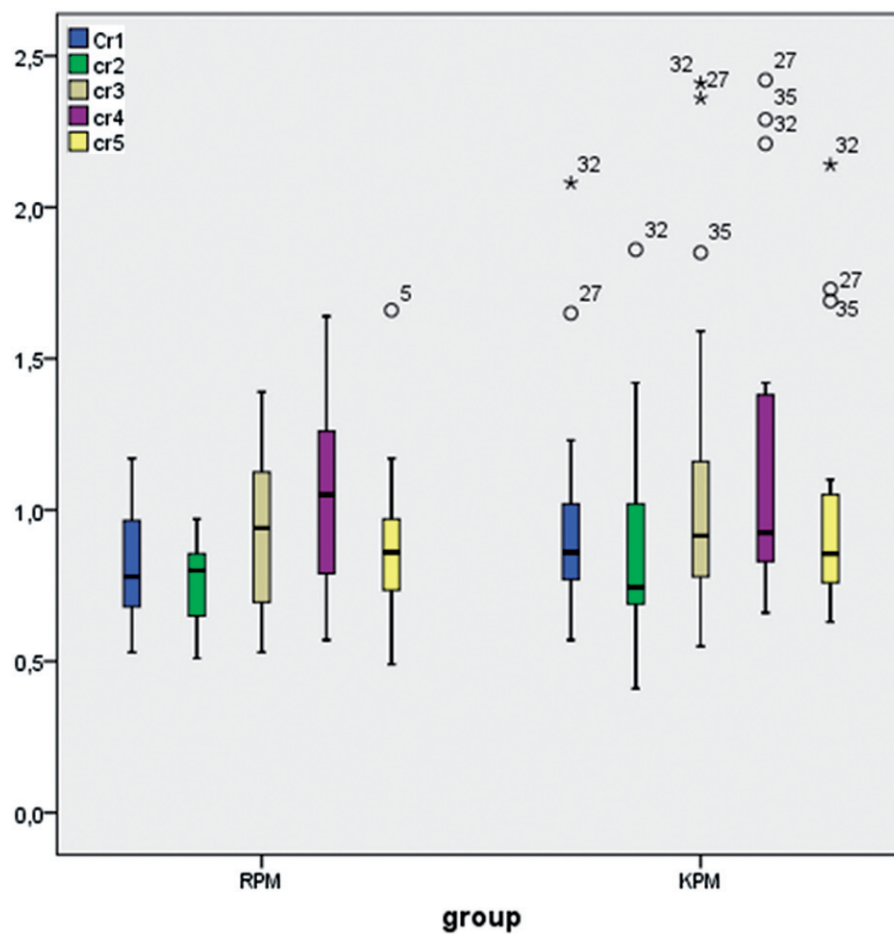
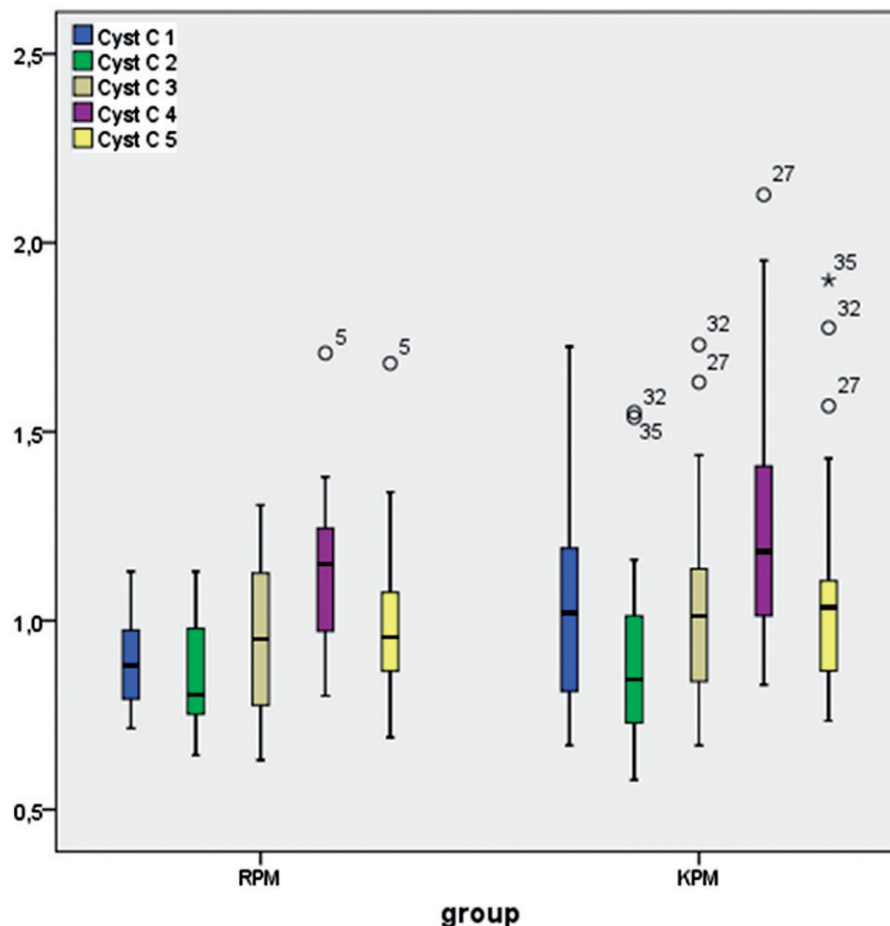


Figure 4. Cystatin-C levels (mgL^{-1}) are presented as box plots for each group and time point. Note: For remifentanyl group: Cystatin-C 1–4 $p < 0.001$, Cystatin-C 2–4 $p < 0.001$, Cystatin-C 3–4 $p < 0.01$. For ketamine group: Cystatin-C 1–4 $p < 0.01$, Cystatin-C 2–4 $p < 0.001$, Cystatin-C 3–4 $p < 0.001$, Cystatin-C 4–5 $p < 0.01$.



High sensitive (Hs)-troponin T was found to be higher in postoperative day 1 samples ($p < 0.05$); there were no significant differences between the remaining groups (Figure 5). In the remifentanyl group baseline Hs-troponin T level (mean $\pm$ SD) was 19 ± 15 ng/L; postoperative first day level was 662 ± 723 ng/L, in ketamine groups baseline Hs-troponin T level was 18 ± 21 ng/L; postoperative first day level was 575 ± 505 ng/L.

Different eGFR formulas using creatinine (MDRD, CKD-EPI, Cockcroft Gault); cystatin-C (eGFR1, eGFR2) or a combination of creatinine and cystatin-C (eGFR 3) were used to calculate eGFR. eGFR1, eGFR2, eGFR3, MDRD, CKD-EPI and Cockcroft Gault levels were similar between the groups and postoperative second day samples were statistically lower than baseline ($p < 0.05$).

Stage 1 AKI, which is known as a dysfunction, was observed in seven patients from the remifentanyl group and six patients from the ketamine group on postoperative day 2. Creatinine values that increased by 0.3 g dL^{-1} or more compared to basal values on postoperative day 2 decreased back on postoperative day 4; none of the patients experienced stage 2 AKI (Table 3).

There was no mortality or morbidity after surgery in both the groups.

Discussion

In the present study, in patients with normal renal functions undergoing on-pump coronary bypass, the effects of use of

ketamine and remifentanyl as anesthetic agents on AKI development were compared by renal biomarkers. The effects of ketamine and remifentanyl on renal functions were found similar. Cystatin-C and eGFR values varied in parallel with classical markers, urea and creatinine. After the surgery, GFR increased; urea, creatinine and cystatin-C decreased in both groups compared to basal values. On postoperative day 1, GFR started to decrease; urea, creatinine and cystatin-C started to increase. On postoperative day 2, after reaching the lowest GFR value, it increased on postoperative day 4, and the values were observed to be close to the basal values. In seven patients from the remifentanyl group and in six patients from the ketamine group, reversible stage 1 AKI, which is known as a dysfunction, was observed on postoperative day 2. It was observed that ketamine use in coronary bypass surgery did not cause any cardiac adverse event.

According to the literature, in on-pump cardiac surgery, ketamine weakens the increase of CRP, IL-6 and IL-8, all of which are proinflammatory cytokines, and causes an increase in anti-inflammatory cytokine IL-10 and thus positively affects the functional outcome.^{8,9,22} The inflammation period, which is an important risk factor for organ dysfunction following major surgeries, is known to be among AKI pathogenesises.^{2,3} The study was based on these premises and it was observed that $1\text{--}3 \text{ mg kg}^{-1}$ ketamine infusion during surgery was not better than remifentanyl infusion in terms of kidney functions. Since the study included only patients with normal basal renal functions, ketamine may not have created detectable effects on healthy kidneys. To identify the renal

Figure 5. Hs-troponin T levels (ng/L) are presented as box plots for each group and time point. Note: Both for groups: Hs-troponin T 1–2 $p < 0.001$, Hs-troponin T 1–3 $p < 0.001$, Hs-troponin T 1–4 $p < 0.001$, Hs-troponin T 1–5 $p < 0.05$, Hs-troponin T 3–5 $p < 0.001$.

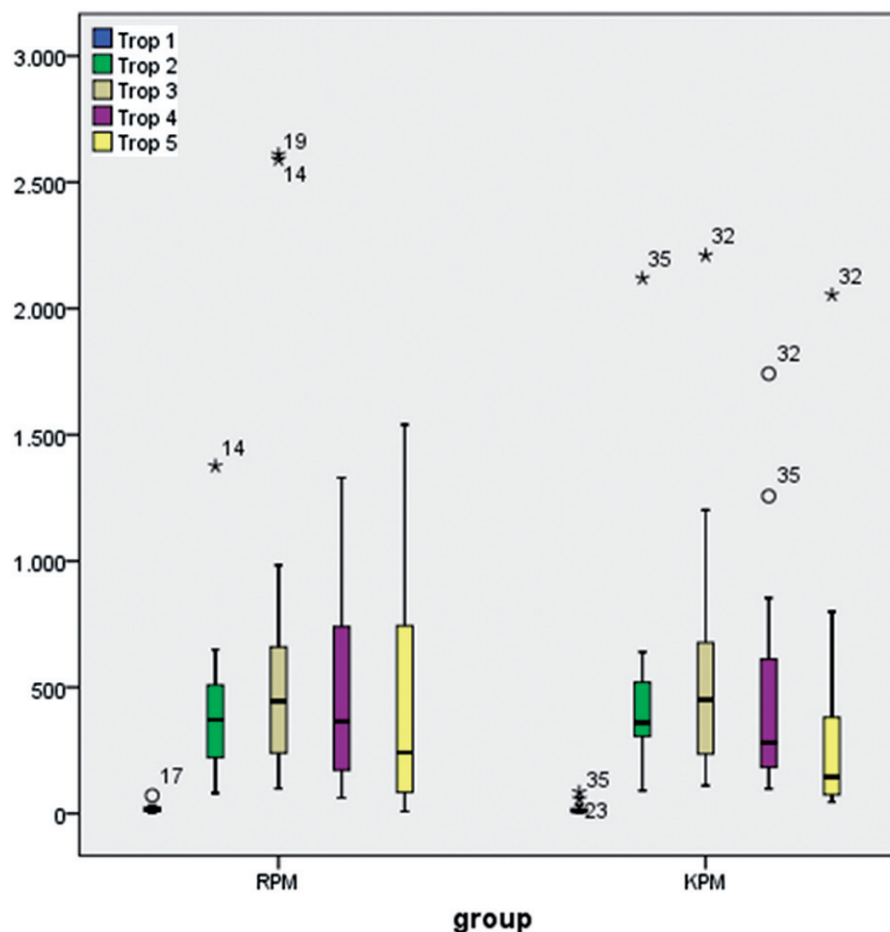


Table 3. Data of the patients with stage 1 AKI in postoperative day 2.

Patients	Age(year)/ Sex (M/F)	DM/ HT	Baseline Cr	Postop. 2.day Cr	Baseline Cys-C	Postop. 2.day Cys-C	Preop. Hct%	Xklemp time	RBC Transf Unit	Preop. statin	Euroscore II
RPM 2	60/M	–/–	0.78	1.10	0.71	1.15	38.8	68	1	+	0.55
RPM 3	55/M	–/–	0.73	1	0.84	1.2	43.8	80	–	+	0.55
RPM 10	66/M	–/–	1.14	1.64	0.99	1.35	38.1	54	–	–	0.66
RPM 11	68/F	+/+	0.62	1.05	0.79	1.29	44.1	38	–	–	1.23
RPM 12	68/F	–/+	0.82	1.21	0.91	1.2	33.8	58	1	+	0.87
RPM 13	66/M	+/+	0.92	1.52	0.88	1.31	36.3	55	1	+	1.28
RPM 19	55/M	–/–	0.72	1.53	0.95	1.15	42.3	51	1	+	0.55
KPM 5	62/M	–/–	0.86	1.12	1.1	1.4	41	97	2	+	0.71
KPM 7	47/M	–/+	0.85	1.38	0.9	1.22	44.8	41	1	–	0.55
KPM 8	51/M	+/-	1.65	2.42	1.5	2.10	36.1	45	–	+	0.79
KPM 9	65/M	–/+	0.69	1.24	0.9	1.13	39.4	52	–	+	0.64
KPM 14	58/M	+/-	0.91	1.26	0.95	1.16	33	45	–	+	1.3
KPM 15	57/M	–/–	1.1	2.29	1.22	1.95	45	60	–	+	0.55

Notes: RPM: remifentanyl-propofol-midazolam; KPM: ketamine-propofol-midazolam. DM: diabetes mellitus; HT: hypertension; Postop: postoperative; Preop: preoperative; Hct: hematocrit; RBC: red blood cell; Cr: creatinin; Cys-C: Cystatin-C.

injury, if IL-18, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), urinary microalbumin, urinary *N*-acetyl- β -glucosaminidase (NAG) and similar markers, all of which increase at various periods during surgery, were used, more detailed physiopathological panel could have been obtained, but it would be a costly method.

It was previously reported in the literature that remifentanyl weakens endocrine stress response and cell-mediated immune response, and shortens the ICU stay.^{23,24} This may be the

reason why no difference between groups was observed. A follow-up study might include cardiac patients with similar renal dysfunctions to compare ketamine and remifentanyl in terms of their immune protective effects determined by more elaborated markers. In the present study, racemic ketamine (*R*-(–)-ketamine) was used. In the literature, it was reported that isomeric *S*-(+)-ketamine had higher analgesic potential and fewer side effects and it was also reported that *S*-(+)-ketamine decreased the coronary adherence of polymorphonuclear neutrophils during postischemic period.¹⁰

Renal effects of these two different ketamine isomers are also worth to investigate.

Due to the limited blood flow in coronary artery patients, the use of medications, such as ketamine, which increases myocardial oxygen demand, causes concerns. In the present study, high sensitive troponin T, which is a very valuable tool, was used to determine if *R*-ketamine use in coronary surgery contributed to myocardial cell damage. Hs-troponin T values increased similarly in both groups after the surgery and decreased in the following days, and no adverse cardiac event was observed. However, it should be noted that patients who are elective and hemodynamically stable were included in the study.

In the present study, cystatin-C and eGFR values varied in parallel with urea and creatinine, which are classical markers, and use of cystatin-C did not yield a quicker result. In the literature, it was reported that plasma use of cystatin-C yields faster results compared to creatinine in detecting renal injury.^{5–7} On the other hand, it was also reported that there is a weak correlation between plasma cystatin-C and creatinine values in individuals with normal healthy renal functions.^{25–27} It was also reported that effects of hemodilution during CPB may still be active in ICU and thus, eGFR values may be confusing.²⁸ In a multi-center study performed by TRIBE-AKI consortium, cystatin-C was found to be less sensitive compared to creatinine in terms of AKI detection.²⁹ In another study, it was reported that eGFR values estimated by combining creatinine and cystatin-C measurement were more accurate.³⁰ In the present study, cystatin-C, creatinine and all related eGFR calculations varied in the same way in all measurement points; therefore, none of them was shown to be better than the other.

According to the AKIN criteria, the minimum 0.3mgdL^{-1} increase in creatinine value within 48 h is considered as stage 1 AKI which is known as a dysfunction.¹ In the present study, in seven patients from the remifentanyl group and in six patients from the ketamine group, transient stage 1 AKI (dysfunction) was observed on postoperative day 2. Creatinine values that increased by 0.3mgdL^{-1} or more compared to basal values on postoperative day 2 decreased back on postoperative day 4; none of the patients experienced stage 2 AKI. In the consortium study of Spahillari, post-cardiac surgery AKI detection time was reported as days 2 and 3; the increases in creatinine and cystatin-C on days 2 and 3 got back to normal values on day 4.²⁹ In the present study, creatinine and cystatin-C values that were increased on day 2 in both groups came close to the basal values on day 4. Since no measurement was performed on day 3, we just guess that there was a decreasing trend. Similarly, Abu-Omar reported that along with plasma creatinine and cystatin-C values, urinary NAG and urinary microalbumin/creatinine values reached peak levels on day 2 following cardiac surgery.³¹ The reason for peak levels on postoperative day 2 may be that oral intake starts for patients discharged from ICU to the general ward and intravenous fluids were reduced. Even though oral intake is started on these patients, the intake is not as much as IV replacement. Furthermore, the detection of the cellular damage caused by inflammatory cascade using markers may be delayed.

Consequently, in patients with normal renal functions undergoing on-pump coronary bypass surgery, effects of ketamine and remifentanyl on renal functions in terms of AKI were found to be similar. It was observed that the use of *R*(–)-ketamine in coronary bypass surgery did not cause a cardiac adverse event.

Declaration of interest

The authors report no conflicts of interest.

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