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ORIGINAL ARTICLE

Remifentanil temporarily improves renal function in adult patients with chronic kidney disease undergoing orthopedic surgery

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Abstract

Purpose The objective of this study was to confirm the renal protective effect of remifentanil-based anesthesia in perioperative adult patients with chronic kidney disease (CKD).

Methods A total of 90 non-dialysis perioperative adult patients with CKD, with preoperative estimated glomerular filtration rate from creatinine (eGFRcreat) values of lower than 50 ml/min/1.73 m^2, who had undergone orthopedic surgery under general anesthesia were retrospectively selected. The subjects were divided into two groups according to whether or not remifentanil was used for anesthesia management: group R, in which remifentanil was used for anesthesia management ($n = 45$), and group NR, in which remifentanil was not used for anesthesia ($n = 45$). eGFRcreat was measured pre-surgery (pre), 7 days after surgery (day-7), and 14 days after surgery (day-14).

Results In group R, both day-7 eGFRcreat (52.2 ± 17.0 ml/min/1.73 m^2) and day-14 eGFRcreat (49.7 ± 15.5 ml/min/1.73 m^2) were significantly higher than the pre eGFRcreat (40.7 ± 7.5 ml/min/1.73 m^2) (day-7: $p < 0.01$; day-14: $p < 0.01$). In group NR, on the other hand, pre eGFRcreat (37.8 ± 7.6 ml/min/1.73 m^2), day-7 eGFRcreat (41.2 ± 10.9 ml/min/1.73 m^2), and day-14 eGFRcreat (40.2 ± 10.5 ml/min/1.73 m^2) values were similar. Furthermore, both day-7 eGFRcreat and day-14 eGFRcreat were significantly higher in group R than in group NR (day-7: $p < 0.01$; day-14: $p < 0.01$).

Conclusions Our findings suggest that anesthesia management using remifentanil may have a renal protective effect in perioperative adult CKD patients undergoing orthopedic surgery.

Keywords Renal protective effect · Remifentanil · Chronic kidney disease (CKD) · Estimated glomerular filtration rate from creatinine (eGFRcreat)

Introduction

According to a survey conducted by the Japanese Society of Nephrology [1], the estimated number of adult patients with chronic kidney disease (CKD) in Japan is approximately 13.3 million (12.9 % of the Japanese adult population). Among these are an estimated 10.98 million (10.64 %) patients with CKD stage G3a–G5 having estimated glomerular filtration rate from creatinine (eGFRcreat, ml/min/1.73 m^2) values of under 60 ml/min/1.73 m^2. Furthermore, the estimated number of CKD patients with eGFRcreat values less than 50 ml/min/1.73 m^2 is 3.17 million (3.07 %) (the CKD Practice Guide 2012 of the Japanese Society of Nephrology recommends nephrologist referral of patients with eGFRcreat values less than 50 ml/min/1.73 m^2) [2]. Imai et al. reported that "the rate of eGFRcreat decline was significantly higher in their study

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patients with initial eGFRcreat values of under 50 ml/min/1.73 m^2" [3].

With the steady increase in the number of CKD patients, it is inevitable that the number of perioperative CKD patients is also increasing. Perioperative acute kidney injury (AKI) has often been reported to occur during or after surgery [4, 5]; for CKD patients, such worsening of renal function is often irreversible, sometimes making dialysis unavoidable. It is, therefore, believed anesthesia management may have a significant effect on perioperative renal function in CKD patients.

In recent years, analgesia-based anesthesia management using remifentanil has been shown to be very useful, because it suppresses surgical stress and maintains hemodynamic stability during the intraoperative period. It has, furthermore, been suggested that remifentanil may have an overall protective effect on organs [6, 7]; it has, for example, been reported that the intraoperative urine flow for patients under general anesthesia using remifentanil was significantly higher than for patients under anesthetic management with agents other than remifentanil [8, 9]. However, there are no reports on the renal protective effects of remifentanil. We therefore conducted a retrospective review to assess the effects of anesthesia management using remifentanil on perioperative renal function in CKD patients undergoing orthopedic surgery and examined the renal protective effect of remifentanil.

Materials and methods

This study was conducted after obtaining the approval of the Human Ethics Committee of Kagoshima University Medical and Dental Hospital. We retrospectively selected 90 adult CKD patients with preoperative eGFRcreat values of less than 50 ml/min/1.73 m^2 who had undergone scheduled orthopedic surgery under general anesthesia between September 2002 and September 2012 at Kagoshima University Medical and Dental Hospital. Patients who were on maintenance dialysis treatment were excluded from the study. The patients were divided into two groups: group R ($n = 45$) in which remifentanil was used for surgical anesthesia management, and group NR ($n = 45$), in which this drug was not used for anesthesia management.

In both groups, the patients were started on mechanical ventilation after tracheal intubation; anesthesia was maintained with sevoflurane, air, and oxygen, and neuromuscular blockade by administration of rocuronium or vecuronium. In some cases, epidural anesthesia or peripheral nerve block was used in addition to general anesthesia. In group R, remifentanil was infused continuously during the surgical period, at doses adjusted continuously according to the vital signs of the patient assessed by the anesthesiologist in charge. Fentanyl was also administered intermittently in all cases.

The following preoperative patient characteristics were compared between the two groups: gender distribution, age, height (cm), weight (kg), American Society of Anesthesiologists' physical status classification (ASA physical status), CKD GFR stage, complications, medications used, systolic blood pressure (SBP, mmHg), heart rate (HR, beats/min), serum creatinine (s-Cr, mg/dl), and eGFRcreat. Furthermore, the following intraoperative patient characteristics were also compared between the two groups: operation time (min), anesthesia time (min), rate of use of epidural anesthesia or peripheral nerve block in combination with general anesthesia, degree of positive fluid balance (+ml), fluid infusion amount (ml), need for blood transfusion, urine output (ml), average SBP, average HR, and average doses of analgesic agents (remifentanil, fentanyl, NSAIDs), volatile inhalational anesthetic agent (sevoflurane), and muscle relaxant (vecuronium, rocuronium).

To monitor renal function, s-Cr levels were measured preoperatively (pre), 7 days after surgery (day-7), and 14 days after surgery (day-14). The eGFRcreat values for each patient at these times were computed from the respective s-Cr values by use of the revised new equation for estimated glomerular filtration rate based on estimated serum creatinine in Japan: eGFRcreat (ml/min/1.73 m^2) = $194 \times \text{Age}^{-0.287} \times \text{S-Cr}^{-1.094}$ (female $\times$ 0.739) [10]. In each group, day-7 eGFRcreat and day-14 eGFRcreat were compared with preoperative eGFRcreat. The eGFRcreat values at each of these times were also compared between the two groups. Furthermore, similar comparisons were made for the s-Cr values, that is, day-7 s-Cr and day-14 s-Cr were compared with preoperative s-Cr for each group, and the s-Cr values at each time-point were compared between the two groups.

Values are expressed as mean ± standard deviation or number of patients (%). For statistical processing, the data for the two groups were compared by use of the chi-squared test, the unpaired t test, or one-way ANOVA, as appropriate. One-way ANOVA with the Tukey–Kramer HSD-test was used for comparison of multiple data. Differences with p values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed using the JMP©8.0.1 statistical software (SAS Institute Japan).

Results

Patient characteristics

There were no statistically significant differences between the preoperative patient characteristics of the two groups (Table 1). There were also no significant differences between intraoperative patient characteristics in the two groups, except for the hemodynamic data, remifentanil use, and rocuronium use, as described below (Table 2).

Table 1 Preoperative patient characteristics

	Group R ($n = 45$)	Group NR ($n = 45$)	p value
Gender (male/female)	23/22	19/26	NS
Age	69.2 ± 8.4	71.8 ± 9.4	NS
Height (cm)	155.2 ± 8.9	153.1 ± 9.2	NS
Body weight (kg)	57.6 ± 10.2	54.6 ± 8.9	NS
ASA PS (n: 1/2/3)	0/34/11	0/32/13	NS
CKD GFR stage (n: G3a/G3b/G4)	21/18/6	11/23/11	NS
Complication			
Hypertension (%)	71 ($n = 32$)	77 ($n = 35$)	NS
Diabetes mellitus (%)	20 ($n = 9$)	20 ($n = 9$)	NS
Ischemic heart disease (%)	33 ($n = 15$)	20 ($n = 9$)	NS
Atrial fibrillation (%)	4 ($n = 2$)	7 ($n = 3$)	NS
Medication			
Ca-channel blocker (%)	53 ($n = 24$)	53 ($n = 24$)	NS
Angiotensin-converting enzyme inhibitor (%)	18 ($n = 8$)	24 ($n = 11$)	NS
Angiotensin receptor blocker (%)	24 ($n = 11$)	16 ($n = 7$)	NS
β-Blocker (%)	22 ($n = 10$)	11 ($n = 5$)	NS
Coronary vasodilator (%)	18 ($n = 8$)	9 ($n = 4$)	NS
Anticoagulant (%)	67 ($n = 18$)	45 ($n = 14$)	NS
Systolic blood pressure[a] (mmHg)	138.4 ± 19.9	142.3 ± 24.0	NS
Heart rate[a] (beats/min)	75.2 ± 12.8	77.0 ± 15.8	NS
s-Cr[b] (mg/dl)	1.27 ± 0.36	1.31 ± 0.36	NS
eGFRcreat[b] (ml/min/1.73 m^2)	40.7 ± 7.5	37.8 ± 7.6	NS

Values are mean ± standard deviation or number of patients (%)

s-Cr, serum creatinine; eGFRcreat, estimated glomerular filtration rate from creatinine; Group R, remifentanil administered in anesthesia management; Group NR, no remifentanil administration

Group R vs. Group NR, using chi-squared test, unpaired t test, one-way ANOVA

[a] Before start of anesthesia

[b] 1–14 days before surgery

Hemodynamic data

The intraoperative average SBP in group R was significantly lower than that in group NR ($p < 0.01$), and the intraoperative average HR was also significantly lower in group R than in the group NR ($p < 0.05$) (Table 2).

Remifentanil and rocuronium

Remifentanil and rocuronium were used only in group R, and the intraoperative average infusion dose of remifentanil in this group was 0.17 ± 0.08 μg/kg/min (Table 2).

Renal function

There were no significant differences between the pre s-Cr or pre eGFRcreat values in the two groups (Table 1). In group R, both the day-7 eGFRcreat value and the day-14 eGFRcreat value were significantly higher than pre eGFRcreat ($p < 0.01$ for both) (Table 3). In group NR, no significant differences were found among pre eGFRcreat, day-7 eGFRcreat, and day-14 eGFRcreat (Table 3). Both the day-7 and day-14 eGFRcreat values were higher in group R than the corresponding values in group NR ($p < 0.01$ for both) (Table 3). With regard to s-Cr values, both the day-7 and day-14 s-Cr values were lower than pre s-Cr in group R, although the difference was not statistically significant for the latter measurement ($p < 0.05$ and NS, respectively) (Table 3). In group NR, on the other hand, no significant differences were found among pre s-Cr, day-7 s-Cr, and day-14 s-Cr (Table 3). Both the day-7 and day-14 s-Cr were lower in group R than in group NR, although the difference was not statistically significant for the latter measurement ($p < 0.05$ and NS, respectively) (Table 3).

Discussion

In this study, both the day-7 and day-14 eGFRcreat values were significantly higher in group R than in group NR (Table 3), and the patient characteristics in the two groups were similar (Tables 1, 2). Therefore, the results of this study showed that anesthesia management using remifentanil, as compared with other methods not involving use of remifentanil, can have renal-protective effects in perioperative adult patients with CKD. Furthermore, in group R, both day-7 eGFRcreat and day-14 eGFRcreat were significantly higher than pre eGFRcreat (Table 3). Thus, this study showed the effect of remifentanil of producing transient improvement of renal function in perioperative CKD patients.

As stated above, this is the first clinical trial to demonstrate the renal protective effect of remifentanil on the basis of perioperative eGFRcreat data (preoperative and postoperative follow-up until 14 days after surgery). Unfortunately, there are no reports yet on the renal-protective effect of remifentanil. In addition, we also did not provide any scientific evidence for the mechanisms underlying the renal-protective effect of remifentanil in this study. Nevertheless, we shall propose two hypotheses of possible underlying mechanisms.

First hypothesis (anti-nociceptive effect of remifentanil): Recent studies indicate the mineralocorticoid receptor (MR) has an important function in the pathophysiology of renal injury; it has been suggested that MR activates

Table 2 Intraoperative patient characteristics

	Group R ($n = 45$)	Group NR ($n = 45$)	p value
Operation time (min)	191.6 ± 119.2	175.8 ± 97.0	NS
Anesthesia time (min)	296.8 ± 135.5	284.2 ± 111.1	NS
Epidural anesthesia or peripheral nerve block (%)	29 ($n = 13$)	38 ($n = 17$)	NS
Positive fluid balance (ml)	1456.2 ± 696.9	1307.8 ± 659.5	NS
Fluid amount (ml)	2210.0 ± 1123.8	2058.9 ± 895.0	NS
Red blood cell transfusion (%)	38 ($n = 17$)	36 ($n = 16$)	NS
Urine output (ml)	566.8 ± 464.5	545.7 ± 346.3	NS
Blood loss (ml)	411.9 ± 770.6	391.3 ± 543.2	NS
Average[a] systolic blood pressure (mmHg)	107.9 ± 13.0	122.2 ± 11.6	<0.01
Average[a] heart rate (beats/min)	72.5 ± 11.1	78.0 ± 11.4	<0.05
Average drug consumption			
Remifentanil (μg/kg/min)	0.17 ± 0.08	–	–
Fentanyl IV (μg/kg)	4.2 ± 2.0	3.7 ± 1.4	NS
Sevoflurane (%)	1.6 ± 0.5	1.8 ± 0.5	NS
Vecuronium (mg/kg)	0.2 ± 0.0 ($n = 14$)	0.2 ± 0.1	NS
Rocuronium (mg/kg)	1.3 ± 0.4 ($n = 30$)	–	–
NSAIDs (mg/kg)	1.1 ± 0.3 ($n = 19$)	1.0 ± 0.2 ($n = 20$)	NS

Values are mean ± standard deviation or number of patients (%)

Group R vs. Group NR, using chi-squared test, unpaired t test, one-way ANOVA

NSAIDs, flurbiprofen

[a] Average of 5-min interval data

Table 3 Changes in perioperative renal function data

	Group	Presurgery[a]	Day-7 after surgery	Day-14 after surgery
s-Cr (mg/dl)	Group R	1.27 ± 0.36	1.07 ± 0.41*,†	1.11 ± 0.42
	Group NR	1.31 ± 0.36	1.24 ± 0.40	1.27 ± 0.39
eGFRcreat (ml/min/1.73 m^2)	Group R	40.7 ± 7.5	52.2 ± 17.0**,††	49.7 ± 15.5**,††
	Group NR	37.8 ± 7.6	41.2 ± 10.9	40.2 ± 10.5

Values are mean ± standard deviation

s-Cr, serum creatinine; eGFRcreat, estimated glomerular filtration rate from creatinine

** $p < 0.01$, * $p < 0.05$, compared with presurgery, by use of ANOVA with Tukey–Kramer HSD-test

†† $p < 0.01$, † $p < 0.05$, Group R compared with Group NR, by use of unpaired t test

[a] Presurgery: 1–14 days before surgery

NADPH oxidase, increases superoxide production, induces oxidative stress, and causes renal injury [11, 12]. Aldosterone is known to activate the MR [11, 12], and in recent years it has been shown that cortisol also activates the MR [12]. In addition, recent clinical studies have indicated the usefulness of MR antagonists and aldosterone antagonists in the management of renal injury [11, 12]. On the other hand, remifentanil has been reported to suppress intraoperative cortisol levels [6] and intraoperative and postoperative aldosterone levels [13]. In this study, average intraoperative SBP and average intraoperative HR in group R were significantly lower than those in group NR (Table 2), suggesting that the anti-nociceptive effect of remifentanil may be responsible for suppression of surgical stress in group R. Thus, the anti-nociceptive effect of remifentanil could lead to suppression of cortisol or aldosterone levels and a consequent decrease in the activation of MR, thereby exerting a protective effect on renal function in perioperative CKD patients.

Second hypothesis (anti-oxidative and anti-inflammatory effects of remifentanil): Oxidative stress and inflammation are now believed to be crucially involved in the pathophysiology of both AKI and CKD [14–17]. Shah et al. reported the importance of oxidants in the pathophysiology and deterioration of CKD [18], and Shankar et al. reported an association between elevated levels of markers of inflammation (tumor necrosis factor-alpha (TNF-α) receptor 2, interleukin-6 (IL-6)) and the risk of development of CKD, suggesting the involvement of inflammatory mechanisms in the etiology of CKD [19]. Furthermore, anti-oxidative or anti-inflammatory agents have been shown to exert protective effects on renal function in patients with AKI and CKD. Interleukin-10 (IL-10) and alpha-melanocyte-stimulating hormone (α-MSH) have been known to act on the proximal renal tubular cells and protect against renal injury [20, 21], and peroxisome proliferator-activated receptor-alpha (PPARα) has been shown to protect proximal renal tubular cells via their anti-oxidative and anti-inflammatory effects [22]. Furthermore, Pergola et al. reported that bardoxolone methyl (an oral antioxidant inflammation modulator: an activator of Nrf2; Nrf2, in turn, which activates the anti-oxidative system) significantly improved renal function (eGFRcreat) in advanced CKD patients with type 2 diabetes [23]. Remifentanil has also been suggested to have anti-oxidative and anti-inflammatory effects. Yang et al. [24] reported that remifentanil increased expression of superoxide dismutase (SOD) and reduced production of reactive oxygen species (ROC), and Ke et al. [25] reported that anesthesia with remifentanil reduced intraoperative IL-6 levels and increased intraoperative IL-10 levels. Thus, the anti-oxidative and anti-inflammatory effects of remifentanil may underlie the effects of this agent in protecting renal function in perioperative CKD patients.

These hypotheses are, however, no more than assumptions, and further studies are required to obtain scientific evidence to explain the effect of remifentanil in protecting the renal function in perioperative CKD patients.

Renal function evaluation: We used eGFRcreat for to evaluate renal function because, at present, eGFRcreat is used to categorize CKD patients into the different stages. CKD staging based on eGFRcreat has also been used for planning therapy for CKD patients [1–3, 10, 26, 27]. Furthermore, because eGFRcreat has been reported to be a highly valid means of evaluation of perioperative renal function [28–30], we afforded eGFRcreat data prominent status in our study.

Study limitations: Because of the retrospective nature of our study, we could not fully match conditions in the two groups (for example different muscle relaxant use); other renal function evaluation criteria, for example cystatin C or urinalysis results (examinations for proteinuria and hematuria), etc., were not assessed, vital reactions associated with surgical stress, for example perioperative stress hormone levels and perioperative blood glucose levels, were not assessed, and the perioperative anti-oxidative and anti-inflammatory indexes were not evaluated. Thus, we could not obtain scientific evidence in support of the mechanisms underlying the effect of remifentanil in protecting renal function for perioperative CKD patients in this study.

In conclusion, this study showed that anesthesia management using remifentanil, as compared with other methods not involving the use of remifentanil, exerted a renal protective effect in perioperative adult patients with CKD undergoing orthopedic surgery. These effects were confirmed to last for at least 2 weeks after the surgery. In addition, this study also suggested that remifentanil actually improved renal function in perioperative adult CKD patients undergoing orthopedic surgery.

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Conflict of interest None of the authors has any conflict of interest to declare.

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