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Full Length Research Paper

Efficacy and safety of parecoxib sodium after renal transplantation

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The analgesic effect and safety of parecoxib sodium in patients after renal transplantation was studied. Forty-eight patients undergoing renal transplantation were recruited and randomly assigned to three groups (n = 16): Control (2 ml normal saline), parecoxib sodium treatment (40 mg) and fentanyl treatment (0.1 mg). Hemodynamic parameters were recorded prior to, at the time of, or after extubation. The visual analogue scale/score (VAS), Ramsay sedation score, blood urea nitrogen (BUN) and serum creatinine levels were recorded. No significant differences for age, gender, weight, length of hospitalization, operation time or intraoperative infusion volume among the three groups (P > 0.05). There were no significant differences (P > 0.05) over time in values of hemodynamic parameters, in the parecoxib sodium treatment group. Parecoxib sodium efficiently improved postoperative analgesia, decreased the incidence of side effects and reduced the number of patients treated with drugs for postoperative analgesia. Parecoxib sodium administration provides stable hemodynamics, improves postoperative conditions and decreases the incidence of side effects in patients receiving renal transplantation without any adverse effects on renal function. Parecoxib sodium might be a candidate drug for postoperative pain relief in patients with renal transplantation.

Key words: Parecoxib sodium, renal transplantation, postoperative pain, postoperative analgesia, hemodynamics.

INTRODUCTION

The worldwide prevalence of end-stage renal disease has continuously increased. Kidney transplantation offers patients with end-stage renal disease the greatest potential for increased longevity and enhanced quality of life (Knoll, 2008). However, surgical injury is usually followed by pain and side-effects, such as cough, nausea and vomiting, which may lead to complications, prolonged length of hospital stay, postoperative fatigue and delayed convalescence (Kehlet, 1999). Improved anesthetic and analgesic management with tight hemodynamic control and pain management contribute to improved short-term and long-term outcomes of renal transplantation (Sprung et al., 2000).

Opioid based analgesic regimens, such as morphine, hydromorphone, oxycodone, codeine, methadone, fentanyl and sufentanil, have been widely used for postoperative pain relief; although, postoperative nausea and vomiting are common side effects of opioids (Watcha and White, 1992; Jorgensen et al., 2000; Dean, 2004). Therefore, development of novel analgesic drugs as well as drug administration strategies are required to efficiently prevent hyperalgesia, inhibit inflammation, reduce pain and decrease the incidence of side effects.

Cyclooxygenase-2 (COX-2) is highly expressed in the area of inflammation and is also involved in pain induction (Seibert et al., 1994). Previous reports showed that pre-operative administration of the COX-2 specific inhibitor

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Abbreviations: ASA, American society of anesthesiologists; **VAS,** visual analogue scale/score; **BUN,** blood urea nitrogen; **HR,** heart rate; **SBP,** systolic blood pressure; **DBP,** diastolic blood pressure; **SPO_2,** pulse oxygen saturation; **CVP,** central venous pressure; **COX-2,** Cyclooxygenase-2; **BMI,** body mass index; **NSAIDs,** non-steroidal anti-inflammatory drugs.

parecoxib sodium (Talley et al., 2000) before oral surgery was effective, safe and well-tolerated for treating post-operative pain (Desjardins et al., 2001). Nevertheless, the analgesic effect and safety of parecoxib sodium in patients undergoing renal transplantation has not been clearly demonstrated.

In the present study, we evaluate the analgesic efficacy, safety and side effect profile of administration of parecoxib sodium in patients with renal transplantation. Our results indicate that intravenous injection of 40 mg parecoxib sodium, 10 min prior to the cessation of anesthetic drug, improved postoperative conditions and decreased the frequency of side effects after renal transplantation, thus providing clinical evidence for the application of parecoxib sodium for postoperative pain relief in patients with renal transplantation.

MATERIALS AND METHODS

Reagents

Parecoxib sodium powder (Cat No. A1PY2) was provided by Pfizer Ltd. (eBeijing, China). Fentanyl (Cat. No. 1007048) was purchased from Yichang Humanwell Pharmaceutical Co., Ltd. (Yichang, Hubei, China). Normal saline (Cat. No. T10123211) was obtained from Sichuan Kelun Pharmaceutical Co. (Chengdu, Sichuan, China).

Patients

Between January, 2009 and March, 2011, 48 patients were randomly selected from the First Hospital of Jilin University, Jilin, Changchun, China. These patients undergoing renal transplantation had American Society of Anesthesiologists (ASA) physical status III or IV. Patient age ranged from 18 to 60 and their body mass index (BMI) was < 28.0 kg/m^2. Patients who had undergone renal transplantation more than once, exhibited digestive tract ulcer with liver dysfunction, or were allergic to non-steroidal anti-inflammatory drugs (NSAIDs) were excluded from this study. All patients abstained from food and water for 6 to 8 h prior to the operation. All participants who met the eligibility criteria were recruited after signing an informed consent. Ethical approval for this study was granted by the First Hospital of Jilin University, Jilin, Changchun, China.

Anesthesia procedure

All the 48 patients received combined intravenous anesthesia using a GE Datex Ohmeda anesthesia machine (Aestiva/5 7900, U.S.A) as previously described (Lv and Li, 2008). Briefly, patients were given 0.04 mg/kg midazolam, 4 μg/kg fentanyl, 0.3 mg/kg etomidate and 0.2 mg/kg cis-atracurium by rapid inducing endotracheal intubation. Anesthesia was maintained with propofol, remifentanil and cis-atracurium during surgery.

Experimental design

Subjects were randomly divided into three groups, with 16 patients per group. For parecoxib sodium treatment, each patient was given 40 mg parecoxib sodium (diluted with normal saline to a final volume of 2 ml) 10 min prior to the cessation of anesthetic drug by intravenous injection. In the fentanyl treatment group, patients received 0.1 mg fentanyl (2 ml). In the control group, each patient was given 2 ml of normal saline. After surgery, when patients felt pain, they were given 100 mg tramadol by intravenous injection. The frequency of tramadol administration as well as the dosage used was recorded.

Hemodynamic evaluation

Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), central venous pressure (CVP) and peripheral oxygen saturation (SpO2, %) were recorded 5 min prior to extubation (T1), at extubation (T2), 5 min after extubation (T3) and 10 min after extubation (T4) by IntelliVue MP-50 Multi-Parameter Patient Monitoring Equipment (M8004A, Philips, U.S.A).

Evaluation of pain level

Postoperative pain level was evaluated using the visual analogue scale/score (VAS) (Price et al., 1983) with a 10 cm length ruler. The patients were asked to point where their pain lay on the scale. Zero represents no pain and 10 is the maximum pain ever experienced by that person.

Evaluation of sedation level

Postoperative sedation level of patients was measured by the Ramsay sedation score (Ramsay et al., 1974), in which 1 = anxious or restless or both, 2 = cooperative, oriented and tranquil, 3 = responding to commands, 4 = brisk response to stimulus, 5 = sluggish response to stimulus and 6 = no response to stimulus. A Ramsay sedation score between 2 and 4 was recognized as normal sedation, whereas a value > 4 was considered to equate to over-sedation.

Determination of blood urea nitrogen (BUN) and serum creatinine level

To determine kidney function, the levels of BUN and serum creatinine were measured pre-operatively and 12 or 36 h post-operatively with kits using a kinetic method of enzymatic analysis and enzymatic sarcosine oxidase method, respectively, according to the manufacturer's instructions (Beijing Erdos Medical Technologies Co. Limited, Beijing, China; Intec Products Inc., Xiamen, Fujian, China).

Statistical analysis

Data were analyzed using SPSS 17.0 software and were plotted as mean ± SD. Comparison between the different groups of subjects was made with *t* test, or chi-square test. $P < 0.05$ was recognized as the level of significance.

RESULTS

Patient demography

To estimate the effects of parecoxib sodium on surgical safety and postoperative pain relief during renal trans-plantation, a widely used analgesic regimen, fentanyl, was applied here as a drug control. A total of 48 patients were randomly assigned to three groups, a control group

Table 1. Patient characteristics and operation details in different groups. Data are expressed as number of patients or mean ± SD. There were no significant differences between the three groups.

	Control (n = 16)	Parecoxib sodium (n = 16)	Fentanyl (n = 16)
Age (years)	36.9 ± 11.0	42.3 ± 10.4	45.4 ± 10.1
Gender (Male/Female)	13/3	9/7	13/3
Weight (kg)	63.1 ± 10.2	59.0 ± 11.5	64.5 ± 8.9
Days of hospitalization (days)	14.6 ± 4.1	14.8 ± 6.7	18.2 ± 11.9
Operation time (min)	132 ± 29	138 ± 29	123 ± 19
Intraoperative infusion (ml)	1641 ± 488	1800 ± 501	1231 ± 255

(n = 16), a parecoxib sodium treatment group (n = 16) and a fentanyl treatment group (n = 16). In the control group, each subject was given 2 ml of normal saline; while in the parecoxib sodium treatment group each patient received 40 mg parecoxib sodium (2 ml). Fentanyl was used as positive analgesic drug control, and each patient was given 0.1 mg fentanyl (2 ml) in this group. As shown in Table 1, there was no significant difference in age, gender, weight, days of hospitalization, operation time or intraoperative infusion volume among patients from the three groups ($P > 0.05$).

Comparison of preoperational changes of hemodynamics in the different groups

Hemodynamic parameters, including SBP, DBP, HR, CVP and SpO2 were recorded 5 min prior to extubation (T1), at extubation (T2), 5 min after extubation (T3) and 10 min after extubation (T4). As shown in Table 2, SBP values of patients in the control group increased greatly at T2, T3 and T4 time points as compared to those at T1 ($P < 0.05$). No significant differences in the values of hemodynamic parameters were found at different time points in the fentanyl treatment group, except that decreased SpO2 level was detected at T3 and T4 ($P < 0.05$ compared with T1). Importantly, there was no significant difference in the values of hemodynamic parameters at different time points in the parecoxib sodium treatment group ($P > 0.05$), suggesting parecoxib sodium administration provides stable hemodynamics during renal transplantation operation.

Parecoxib sodium improved postoperative analgesia after renal transplantation

We next estimated the postoperative analgesia and sedation status among the different groups. The postoperative pain level was measured by using the VAS assay. We did not find any statistical difference in the postoperative analgesia status between the fentanyl treatment group and the control group, whereas parecoxib sodium application dramatically reduced postoperative pain level (Figure 1). Nevertheless, according to the data obtained from the Ramsay sedation score, administration of fentanyl significantly decreased the postoperative sedation level as compared to that in the parecoxib sodium or control groups. Therefore, parecoxib sodium efficiently improved postoperative analgesia but not sedation in patients receiving a renal transplant.

Parecoxib sodium decreased the incidence of side-effects after renal transplantation

The incidence of side-effects, such as cough, restlessness, nausea and vomiting, were compared among different experimental groups. Table 3 revealed that parecoxib sodium or fentanyl administration efficiently decreased the incidence of cough and restlessness as compared to control (Control group, 68.75%; parecoxib sodium treatment group, 0; fentanyl treatment group, 18.75%) ($P < 0.05$). Neither parecoxib sodium nor fentanyl significantly decreased the incidence of nausea and vomiting (control group, 12.5%; parecoxib sodium treatment group, 0; fentanyl treatment group, 18.75%) ($P > 0.05$). In addition, compared to the control group, parecoxib sodium or fentanyl treatment significantly decreased the use of drugs for postoperative analgesia (control group, 62.5%; parecoxib sodium treatment group, 0; fentanyl treatment group, 6.25%) ($P < 0.05$). These results indicate that parecoxib sodium had the ability to decrease the incidence of side effects after renal transplantation.

Comparison of the kidney function after surgery

To further determine the safety of parecoxib sodium administration in patients after renal transplantation, kidney function in patients from different groups was estimated. Neither parecoxib sodium nor fentanyl induced any significant differences in postoperative urine volume and preoperative or postoperative BUN or serum creatinine levels, implying that the application of parecoxib sodium or fentanyl is quite safe in patients undergoing renal transplantation.

Table 2. Hemodynamic parameters in patients from different groups. Data are expressed as mean ± SD.

	Control (n = 16)	Parecoxib sodium (n = 16)	Fentanyl (n = 16)
SBP (mm Hg)			
T1	159 ± 10	164 ± 9	158 ± 16
T2	168 ± 11*	163 ± 11	163 ± 17
T3	171 ± 10*	162 ± 11	164 ± 16
T4	167 ± 11*	163 ± 11	161 ± 16
DBP (mm Hg)			
T1	90.1 ± 12.0	88.9 ± 8.6	85.3 ± 8.8
T2	92.8 ± 11.3	87.3 ± 8.9	88.1 ± 8.1
T3	94.6 ± 10.7	87.3 ± 9.4	89.1 ± 6.9
T4	93.4 ± 8.9	86.2 ± 9.6	98.6 ± 6.3
HR (bpm)			
T1	82.9 ± 11.2	81.1 ± 10.9	84.7 ± 9.0
T2	87.5 ± 11.5	83.0 ± 11.9	88.4 ± 8.2
T3	90.8 ± 10.6	82.2 ± 11.3	90.1 ± 8.2
T4	88.4 ± 9.7	80.6 ± 10.0	87.9 ± 8.0
CVP (mm Hg)			
T1	11.6 ± 3.2	12.1 ± 1.9	11.2 ± 2.3
T2	12.4 ± 3.3	12.0 ± 2.0	11.8 ± 2.6
T3	12.4 ± 3.5	12.0 ± 1.9	11.6 ± 2.1
T4	12.2 ± 3.4	11.8 ± 1.9	11.4 ± 2.0
SpO2 (%)			
T1	98.8 ± 1.4	99.4 ± 0.6	99.8 ± 0.4
T2	98.8 ± 1.4	99.4 ± 0.5	99.6 ± 0.5
T3	99.1 ± 1.3	99.4 ± 0.5	98.3 ± 0.4*
T4	99.1 ± 1.1	99.6 ± 0.5	98.7 ± 0.5*

*P < 0.05 compared with T1.

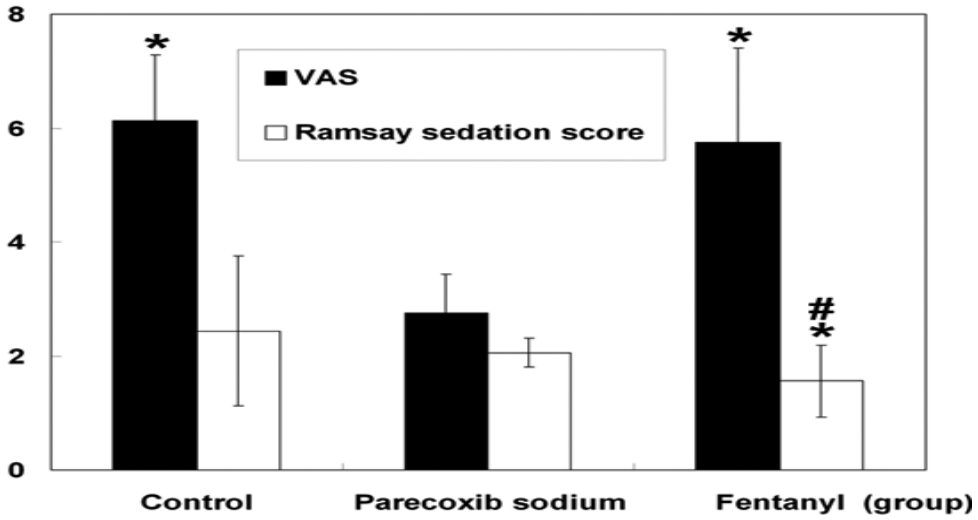

Figure 1. Means of the VAS and Ramsay sedation score for patients from different groups. *P < 0.05 compared with the parecoxib sodium group; #P < 0.05 compared with the fentanyl group.

Table 3. Incidence of cough, restlessness, nausea, vomiting and the number of patients treated with drugs for postoperative analgesia in different groups.

	Cough and restlessness	Nausea and vomiting	Drugs used for postoperative analgesia
Control (n = 16)	11*#	2	10*#
Parecoxib sodium (n = 16)	0	0	0
Fentanyl (n = 16)	3	3	1

Data are expressed as number of patients. *P < 0.05 compared with the parecoxib sodium group; #*P* < 0.05 compared with the fentanyl group.

DISCUSSION

Anesthetic and analgesic approaches that reduce postoperative pain and side-effects, including cough, nausea, vomiting and fatigue, may reduce postoperative morbidity, duration of hospitalization, and hospital costs (Kehlet, 1999). It has been widely accepted that application of intraoperative and postoperative epidural local anesthetics with blockade of both nociceptive afferent and sympathetic efferent nerves may reduce pain and preoperative opioid requirements and improve bowel motility through blockade of the spinal reflex arc (Wattwil et al., 1989; Asantila et al., 1991). Administration of analgesic drugs accompanied with or after anesthetic procedures is needed to efficiently prevent hyperalgesia, inhibit inflammation, reduce pain and decrease incidences of side effects. Opioids, such as morphine, hydromorphone, oxycodone, codeine, methadone, fentanyl and sufentanil are the most widely used regimens for postoperative pain relief (Watcha and White, 1992; Jorgensen et al., 2000; Dean, 2004). Nevertheless, postoperative pain after renal transplantation is believed to be severe and the administration of systemic analgesia could be limited due to impaired renal function and respiratory complications from opioids (Dean, 2004). Therefore, well-controlled analgesic management seems to be critical for improved outcomes of renal transplantation.

In the current study, the analgesic effect and safety of the specific COX-2 inhibitor parecoxib sodium were examined in patients after renal transplantation. Parecoxib sodium, which is hydrolyzed in the liver to the active moiety valdecoxib, has an elimination half-life of approximately 8 h (Karim et al., 2000). It has been reported that parecoxib sodium is well tolerated in humans at doses up to 40 mg by intramuscular injection or 200 mg by intravenous injection (Karim et al., 2000). A previous study revealed that intravenous injection of 20, 40 or 80 mg parecoxib sodium was consistently and significantly superior to administration of placebo in pain intensity, patient global assessments, proportion of patients requiring rescue medication and time to rescue medication (Desjardins et al., 2001). Furthermore, the analgesic effect of preoperatively administered parecoxib sodium reached a plateau at 40 mg (Desjardins et al., 2001). The efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery was tested previously (Barton et al., 2002). Single intravenous doses of parecoxib sodium (20 and 40 mg) had comparable analgesic effects and were well tolerated after laparotomy surgery (Barton et al., 2002). Moreover, parecoxib sodium was as effective as intravenous ketorolac (30 mg) and superior to intravenous morphine (4 mg) (Barton et al., 2002). Additionally, in patients receiving total hip arthroplasty, parecoxib sodium (40 mg) plus morphine demonstrated a significantly lower incidence of fever and vomiting as compared to placebo plus morphine (Malan et al., 2003). Therefore, in the present study, we evaluated the effect of parecoxib sodium on postoperative pain relief during renal transplantation by using the dosage of 40 mg.

There were no statistically significant differences in age, gender, weight, days of hospitalization, operation time or intraoperative infusion volume among patients from parecoxib sodium treatment, fentanyl treatment and control groups (P > 0.05) (Table 1). The SBP values of patients in the control group were greatly increased at T2, or after extubation (T3 and T4) when compared with 5 min prior to extubation (T1) (P < 0.05), suggesting the effects of anesthetic drugs were gradually decreasing with time. However, we cannot rule out the possibility that the reduced SBP level was due to the intolerance of conscious patients to endotracheal intubation. In the fentanyl treatment group, decreased SpO2 level was detected at T3 and T4 (P < 0.05 when compared with T1), implying fentanyl may lead to adverse effects, such as respiratory inhibition in patients during renal transplantation. Notably, there were no significant differences in the values of hemodynamic parameters at different time points in the parecoxib sodium treatment group (P > 0.05), suggesting that parecoxib sodium administration provides stable hemodynamics during renal transplantation operation. However, other studies indicated that selective COX-2 inhibitors, such as rofecoxib and celecoxib, had mild and transient effects on renal blood flow and sodium excretion in salt-depleted or elderly patients (Rossat et al., 1999; Schwartz et al., 2002). Some trials showed that COX-2 inhibitors, such as coxibs and rofecoxib, could increase blood pressure (Whelton, 2002; Whelton et al., 2002; Aw et al., 2005). Hence, the choice of COX-2 inhibitors should be made cautiously and the renal safety profile of these inhibitors should be fully documented.

Table 4. Comparison of the kidney function in patients from different groups.

	Control (n = 16)	Parecoxib sodium (n = 16)	Fentanyl (n = 16)
Urine volume (ml)			
12 h postoperation	807 ± 462	802 ± 422	630 ± 403
36 h postoperation	11853 ± 3240	11676 ± 3479	11354 ± 3563
BUN (mM)			
Preoperation	849 ± 20	904 ± 18	875 ± 18
12 h postoperation	204 ±21	184.9±24.4	170 ± 28
36 h postoperation	114 ± 21	134 ± 22	126 ± 23
Creatinine (μM)			
Preoperation	14.3 ± 2.3	15.8 ± 2.1	16.0 ± 2.8
12 h postoperation	10.9 ± 2.8	10.5 ± 2.1	9.7 ± 2.0
36 h postoperation	6.8 ± 3.1	6.0 ± 2.1	6.2 ± 2.6

Data are expressed as mean ± SD. There were no significant differences between the three groups.

As revealed by VAS analysis, no statistical differences were detected in the postoperative analgesia status between the fentanyl treatment and control groups, whereas parecoxib sodium application dramatically reduced the postoperative pain level in patients with renal transplantation (Figure 1), suggesting the efficacy of parecoxib sodium in postoperative pain relief. COX-2 is expressed throughout the nervous system and participates in pain sensitivity. It catalyzes the conversion of free arachidonic acid (AA) to the short-lived prostanoid precursor prostaglandin H2 (PGH2), which is then converted to prostaglandin E2 (PGE2) (Bazan, 2001). Prostanoids lead to increased excitability and a reduced pain threshold. Meanwhile, COX-2 is reported to be dramatically upregulated at the site of inflammation (Crofford, 1997). Surgical injury may lead to the release of inflammatory factors and promote the increase in COX-2 activity. Therefore, COX-2 blockade by specific COX-2 inhibitors is a candidate treatment for pain relief. Parecoxib sodium exerts its anti-inflammatory and analgesic activity by suppressing the expression of COX-2 and subsequently reducing the synthesis of PGE2.

Among 16 patients from the control group, 11 patients exhibited side effects including coughing and restlessness, two patients had nausea and vomiting and 10 patients were injected with 100 mg of tramadol after surgery. Fentanyl decreased the incidence of these side effects. Importantly, none of the patients presented any side effects mentioned earlier and none needed the administration of tramadol postoperation. These results indicated that parecoxib sodium administration is superior to application of fentanyl in preventing postoperative side effects, including cough, restlessness, nausea and vomiting, and the proportion of patients requiring rescue medication.

Emerging research shows that COX-2 inhibition by specific inhibitors may influence renal function. Schwartz et al. (2002) reported that daily urinary sodium excretion during the first 72 h of administration was dramatically decreased in rofecoxib and celecoxib treatment groups when compared with baseline ($P < \text{or} = 0.05$). Moreover, celecoxib had a short-term transient effect on reducing glomerular filtration rate, urine output ($P < 0.05$), and sodium, lithium and potassium excretion ($P < 0.01$) (Rossat et al., 1999). Hence, we determined the effects of parecoxib sodium administration on kidney function in patients undergoing renal transplantation. Although, various indexes have been used for evaluating renal function (Bokenkamp et al., 1998; Bostom and Dworkin, 2000; Zhang et al., 2003; Tian et al., 2005; Yi and Wang, 2007), serum creatinine and BUN level are the most common endogenous markers (Rule et al., 2004; Kirtane et al., 2005). To assess the safety of parecoxib sodium administration in patients after renal transplantation, kidney function in patients from different groups was examined. Neither parecoxib sodium nor fentanyl induced any significant differences in postoperative urine volume or preoperative or postoperative BUN and serum creatinine levels, implying parecoxib sodium and fentanyl do not affect glomerular filtration rates. Therefore, the application of parecoxib sodium or fentanyl is quite safe in patients undergoing renal transplantation. In addition, urine output was recorded in the first 36 h after surgery. One patient in the control group had delayed urine flow at the beginning of transplantation and one patient in the fentanyl treatment group exhibited vasospasm during kidney transplantation. It is unclear as to whether or not the incidence of such adverse effects was due to the administration of analgesic drugs. Although, no statistically significant differences were found in postoperative urine flow among the three treatment groups ($P > 0.05$), a slight increase in urine output volume at 36 h after surgery was observed in the parecoxib sodium treatment group when compared with the fentanyl treatment group (Table 4). These data suggest that parecoxib sodium may have little or no

influence on renal function. However, we could not exclude the possibility that these results were drawn from a limited sample size. Future studies will be performed to investigate the effects of parecoxib sodium on kidney function by enlarging the sample size and extending the monitoring period.

In conclusion, intravenous injection of 40 mg parecoxib sodium 10 min prior to the cessation of anesthetic drug demonstrated fewer side effects and is preferable to fentanyl for patients undergoing renal transplantation surgery. However, the use of parecoxib sodium on the postoperative recovery of the patients after renal transplantation is unclear. Moreover, the optimal mode, dose and timing of parecoxib sodium administration need further investigation.

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