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# Perioperative Ketorolac Use: A Potential Risk Factor for Renal Dysfunction After Live-Donor Nephrectomy

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Data Interpretation D
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**Background:** Ketorolac is a nonsteroidal anti-inflammatory drug indicated for pain control after surgeries in many fields. The aim of this study was to evaluate the impact of ketorolac use after live-donor nephrectomy (LDN).

**Material/Methods:** We reviewed data on 251 patients who underwent laparoscopic LDN from April 2008 to March 2016. Ketorolac was given to 167 patients intraoperatively or postoperatively within 24 h after LDN. Glomerular filtration rate (GFR) percentage was defined as postoperative GFR/preoperative GFR. GFR and GFR percentage at 2 weeks, 6 months, and 1 year after LDN were compared between patients with and without ketorolac administration. Multivariate analysis was performed to identify risk factors for low GFR percentage 1 year after LDN.

**Results:** GFR at 1 year was significantly lower in patients who received ketorolac than in those who did not (62 ml/min/1.73 $m^2$ *vs.* 73 ml/min/1.73 $m^2$, $P<0.01$). The differences in GFR and GFR percentage between 2 weeks and 1 year after LDN was significantly lower in the ketorolac group (GFR; 3.0 ml/min/1.73 $m^2$ *vs.* 14.0 ml/min/1.73 $m^2$, $P<0.01$; GFR percentage; 2.0% *vs.* 12.0%, $P<0.01$). Urinary albumin/creatinine ratio 1 year after LDN was significantly higher in the ketorolac group compared to the non-ketorolac group (8.6 mg/g *vs.* 12.6 mg/g, $P=0.02$). Multivariate analysis revealed that ketorolac use was an independent risk factor for low GFR percentage 1 year after LDN (odds ratio 1.38).

**Conclusions:** Ketorolac appears to be a risk factor for renal dysfunction in the long term after LDN. Prospective clinical trials are needed to reassess its safety.

**MeSH Keywords:** **Glomerular Filtration Rate • Ketorolac • Nephrectomy • Renal Insufficiency, Chronic**

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## Background

Living donor kidney transplantation is currently an important treatment option for patients with end-stage renal disease (ESRD) [1]. Living donors supply approximately 40% of renal allografts in the United States (US) [2]. One of the reasons for the shortage of living donors is the fear of surgical complications caused by a procedure in which the donor has no personal medical benefit. Perioperative mortality after live-donor nephrectomy (LDN) is approximately 3 per 10 000 cases, and major and minor perioperative complications affect approximately 6% and 22% of donors, respectively [2]. Some studies reported that long-term risk of ESRD after living kidney donation was higher in living kidney donors compared to healthy matched non-donors [3,4]. however, the magnitude of the absolute risk increase was small [4].

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) indicated for short-term management of acute pain requiring analgesia at the opioid level [5]. It has been used extensively for its perioperative analgesic effects in abdominal, gynecological, oral, orthopedic, and urological fields [6,7]. Previous studies have established the safety of ketorolac administration postoperatively after LDN and have reported decreased opioid requirements, a quicker return of bowel function, and shorter hospital stay, and it is widely used in many transplant centers in the USA [8–10]. However, few studies have focused on long-term outcome after LDN [11,12].

The aim of this study was to evaluate the impact of ketorolac use after laparoscopic LDN. The pain scores immediately and postoperatively at 24 h, length of hospital stay (LOS), and glomerular filtration rates (GFR) and postoperative GFR percentage at 2 weeks, 6 months, and 1 year after LDN were compared between patients with and without ketorolac administration. Furthermore, we performed a multivariate analysis to assess risk factors for reduction of GFR at 1 year after LDN.

## Material and Methods

### Study population

Between April 2008 and March 2016, 259 patients underwent LDN at the Department of Transplant and Hepatobiliary Surgery, Henry Ford Hospital. Eight patients who underwent open nephrectomy were excluded from analysis. Thus, a final population of 251 recipients who underwent laparoscopic LDN was enrolled in this study. All data collection was approved by the Henry Ford Hospital Review Board.

### Operative procedures and organ preservation

*Hand-assisted laparoscopic nephrectomy is as follows*

The donor is placed in the lateral position. An 8-cm midline incision is made around the umbilicus, and a hand port device (Applied GelPort; Applied Medical, Rancho Santa Margarita, CA) is inserted. A 12-mm camera trocar is placed at the epigastric area. Under direct vision and hand guidance, 1 additional working laparoscopic port is inserted. The peritoneal cavity is insufflated with carbon dioxide to a pressure of 15 mmHg and the urine output is maintained throughout the surgery by administering intravenous fluids. The gonadal, adrenal, and lumbar veins are ligated using surgical clips (Endoclip; Ethicon, Irvine, CA). Initial posterior and inferior dissection of the hilum is performed, and anterior and superior dissection is performed to completely free the hilum. After the ureter is transected, the renal artery is transected using a liner stapler (Multifire Endo TA 30 Stapler, Covidien, Mansfield, MA) and surgical clips, and the renal vein is separated using the liner stapler (Endopath ETS articulating linear cutters; Ethicon, Irvine, CA).

*Robotic-assisted laparoscopic nephrectomy is as follows*

The donor is placed in the lateral position. An 8-cm midline incision is made around the umbilicus, and a hand port device is inserted. The procedure is then performed completely robotically, using the da Vinci® system (Intuitive Surgical, Sunnyvale, California). The surgeon is seated at a remote console after the robotic arms are docked to the trocars. The procedure then follows a transperitoneal approach. Ligation and stapling of the ureter and vasculature are the same as in the laparoscopic hand-assisted procedure. The organ is extracted through the incision, placed on ice, and flushed with cold histidine-tryptophan-ketoglutarate solution.

### Pain control for ketorolac use and pain score.

Patients received ketorolac 15 or 30 mg intravenously intraoperatively at the end of LDN. Patients received ketorolac postoperatively within 24 h after surgery. Indication of ketorolac use was based on the surgeon`s preference. Simultaneously, patients received narcotics depending on their allergy status and adverse effects. There was no use of patient-controlled analgesia. Pain scores were assessed using subjective scoring by a numeric rating scale (maximum 10).

### Calculation of GFR, postoperative GFR percentage, and urinary albumin/creatinine ratio (UACR)

GFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation. This equation was selected because it has been shown to be a more accurate



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estimation of GFR in healthy patients than the Modification of Diet in Renal Disease equation, which was developed using data from a study population with chronic kidney disease (CKD) and thus often underestimates GFR in those with normal renal function [13]. GFR percentage was defined as postoperative GFR/preoperative GFR.

UACR, a surrogate marker for CKD, was studied prior to and 1 year after LDN.

### Postoperative patient follow-up

Patients were followed in the outpatient clinic at 2 weeks, 6 months, and 1 year after LDN. All patients were preoperatively informed about the risk of developing ESRD and educated not to use over-the-counter NSAIDs.

### Statistics

Results are presented as numbers and percentages, and groups were compared using the chi-square test or Fisher's exact test. Continuous variables are expressed as median and interquartile range, and groups were compared using the unpaired *t* test. Univariate and multivariate logistic regression analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL). All variables with $P<0.10$ in univariate analyses were included in a multivariate logistic regression analysis. Statistical significance was considered at $P<0.05$.

## Results

### Demographics

Ketorolac was given to 167 patients intraoperatively and/or postoperatively within 24 h after LDN, and 84 patients were managed without ketorolac. Distribution of dose of ketorolac use is depicted as a bell-shaped standard distribution curve (Figure 1). The median use dose was 45 mg (0–60 mg). There were no differences in age, sex, ethnicity, smoking history, comorbidities, body mass index, side of kidney removed, remnant kidney size, warm ischemia time, or estimated blood loss between the ketorolac and non-ketorolac groups (Table 1). Preoperative creatinine (CR) level was significantly lower in the non-ketorolac group (0.80 mg/dl *vs.* 0.71 mg/dl, $P=0.02$), but there was no difference in preoperative GFR between the 2 groups (108 ml/min/1.73 m$^2$ *vs.* 110 ml/min/1.73 m$^2$, $P=0.20$, Table 1).

### LOS and pain scores immediately and 24 h after LDN

LOS was significantly shorter in patients with ketorolac than patients without ketorolac (3.3 *vs.* 2.8 days, $P=0.03$, Table 2). There was no association with the drug doses.

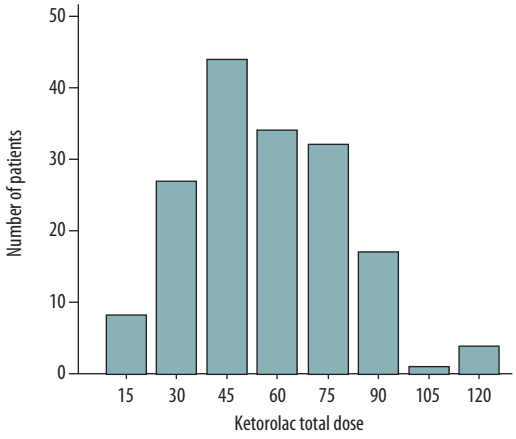


**Figure 1.** Distribution of dose of ketorolac use. Dose of ketorolac use is depicted as a bell-shaped standard distribution curve.

The pain scores 24 h after LDN were significantly lower in the ketorolac group compared to the non-ketorolac group (4.6 *vs.* 3.2, $P<0.01$). When patients were classified by intraoperative ketorolac use, the pain score was significantly lower immediately after LDN in patients with intraoperative ketorolac use (4.2 *vs.* 3.0, $P=0.03$, Table 2). When patients were classified by use dose 0 mg, 15–60 mg, and 75–120 mg, the pain scores 24 h after LDN showed reduction in a dose-dependent manner (4.6 *vs.* 3.4 *vs.* 2.6, $P<0.01$, Table 2).

### Postoperative GFR and GFR percentages 2 weeks, 6 months, and 1 year after LDN

GFR 6 months after LDN tended to be lower in patients with ketorolac than patients without ketorolac, but this was not significant (62 ml/min/1.73 m$^2$ *vs.* 68 ml/min/1.73 m$^2$, $P=0.10$, Figure 2). On the other hand, GFR at 1 year was significantly lower in patients with ketorolac (62 ml/min/1.73 m$^2$ *vs.* 73 ml/min/1.73 m$^2$, $P<0.01$, Figure 2). Furthermore, both GFR percentage at 6 months and 1 year after LDN was significantly lower in the ketorolac group (2 weeks: 52% *vs.* 55%, $P=0.09$; 6 months: 55% *vs.* 64%, $P=0.01$, 1 year: 55% *vs.* 69%, $P<0.01$, Figure 3).

The difference of GFR and GFR percentage between 14 days and 1 year after LDN was significantly lower in the ketorolac group (GFR; 3.0 ml/min/1.73 m$^2$ *vs.* 14.0 ml/min/1.73 m$^2$, $P<0.01$; GFR percentage 2.0% *vs.* 12.0%, $P<0.01$).

### UACR before LDN and 1 year after LDN

Despite no difference in UACR prior to LDN (8.9 mg/g *vs.* 8.8 mg/g, $P=0.89$), UACR at 1 year was significantly higher in


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**Table 1.** Demographics.

| | Ketorolac use | | | | *P* |
|---|---|---|---|---|---|
| | No (N=84) | | Yes (N=167) | | |
| **Background factors** | | | | | |
| Age (years) | 42 | (33–49) | 43 | (34–51) | 0.68 |
| Gender, female (%) | 49 | (58%) | 108 | (65%) | 0.28 |
| Ethnicity | | | | | |
| Caucasian, (%) | 58 | (68%) | 122 | (73%) | 0.63 |
| African American, (%) | 19 | (22%) | 29 | (17%) | |
| Others, (%) | 9 | (10%) | 16 | (9%) | |
| Smoking within 6 months, yes (%) | 8 | (9%) | 28 | (17%) | 0.12 |
| Comorbidity | | | | | |
| Hypertension, yes (%) | 9 | (10%) | 9 | (5%) | 0.13 |
| Diabetes, yes (%) | 0 | (0%) | 1 | (0.5%) | 0.47 |
| Hyperlipidemia, yes (%) | 7 | (8.2%) | 6 | (3.6%) | 0.33 |
| BMI (kg/m$^2$) | 27.5 | (24.6–30.1) | 27.5 | (24.3–31.8) | 0.80 |
| **Surgical factors** | | | | | |
| Type of nephrectomy | | | | | 0.11 |
| Laparoscopic | 81 | (95%) | 149 | (89%) | |
| Robotic | 4 | (5%) | 18 | (11%) | |
| Side of nephrectomy | | | | | 0.83 |
| Left | 83 | (98%) | 163 | (98%) | |
| Right | 2 | (2%) | 4 | (2%) | |
| Remnant kidney size (cm) | 11.1 | (10.5–11.9) | 11.2 | (10.6–11.7) | 0.56 |
| Renal artery ligated | 1 | (1–2) | 1 | (1–1) | 0.58 |
| Operative time (min) | 260 | (215–297) | 250 | (220–275) | 0.09 |
| Estimated blood loss (ml) | 50 | (50–100) | 50 | (39–100) | 0.31 |
| **Kidney function** | | | | | |
| Preoperative serum CR (mg/dl) | 0.80 | (0.61–0.90) | 0.71 | (0.58–0.88) | 0.02 |
| Preoperative GFR (ml/min/1.73 m$^2$) | 108 | (84–129) | 110 | (92–137) | 0.20 |

BMI – body mass index; CR – creatinine; GFR – glomerular filtration rate.

patients with ketorolac than patients without ketorolac (8.6 mg/g *vs.* 12.6 mg/g, *P*=0.02, Figure 4).

### Prediction of GFR percentage <49% of the preoperative levels at 1 year after LDN

We set the cutoff level of GFR percentage as 49% because it was in the 25$^{th}$ percentile of the total GFR percentage 1 year after LDN. Table 3 compares the risk factors for GFR percentage <49% at 1 year by a univariate analysis. Ketorolac use (per 15 mg up), female, preoperative medical history of hypertension, and intraoperative lowest mean arterial pressure <60 mmHg were associated with GFR <49% (*P* <0.10) by univariate analysis. A multivariate logistic regression analysis was performed with the above variables. Ketorolac use (odds ratio (OR) 1.38, per 15 mg up, *P*=0.001), female sex (OR 3.02, *P*=0.01), preoperative medical history of hypertension (OR 4.72, *P*=0.01), and intraoperative lowest mean arterial pressure <60 mmHg (OR 3.42, *P*=0.02) became independent risk factors for GFR <49% percentage at 1 year after LDN.

## Discussion

The novelty of this study is that ketorolac appeared to be a risk factor for renal dysfunction in the long term after LDN.



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**Table 2.** Length of hospital stay and pain scores.

| Length of hospital stay (days) | | | | | |
|---|---|---|---|---|---|
| **Ketorolac use during admission** | | **Intraoperative ketorolac use** | | **Dose of ketorolac** | |
| No (n=84) | 3.3 | No (n=182) | 3.0 | 0 mg (n=84) | 3.3 |
| Yes (n=167) | 2.8 | Yes (n=69) | 2.8 | 15–60 mg (n=113) | 2.8 |
| | | | | 75–120 mg (n=54) | 2.9 |
| *P* | **0.02** | *P* | **0.41** | *P* | **0.05** |

| Pain scores (out of 10) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Ketorolac use during admission** | | | **Intraoperative ketorolac use** | | | **Dose of ketorolac** | | |
| | **0 hr** | **24 hrs** | | **0 hr** | **24 hrs** | | **0 hr** | **24 hrs** |
| No (n=84) | 4.2 | 3.2 | No (n=182) | 3.0 | 3.2 | 0 mg (n=84) | 3.2 | 4.6 |
| Yes (n=167) | 3.2 | 4.6 | Yes (n=69) | 4.2 | 3.8 | 15–60 mg (n=113) | 4.4 | 3.4 |
| | | | | | | 75–120 mg (n=54) | 3.7 | 2.6 |
| *P* | **0.23** | **<0.01** | *P* | **0.02** | **0.10** | *P* | **0.03** | **<0.01** |

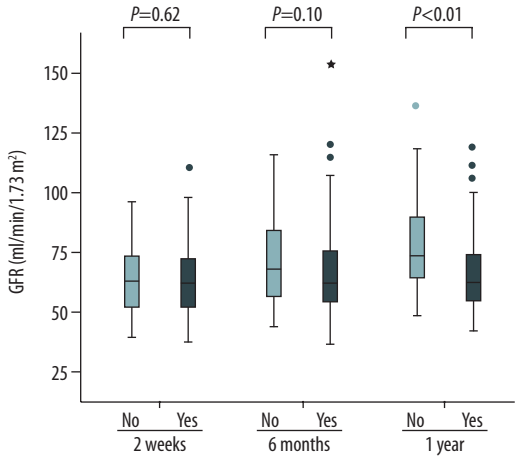


**Figure 2.** Postoperative glomerular filtration rate (GFR) classified by perioperative ketorolac use. Despite no difference in GFR 2 weeks and 6 months after living donor nephrectomy, GFR at 1 year was significantly lower in the ketorolac group than in the non-ketorolac group.

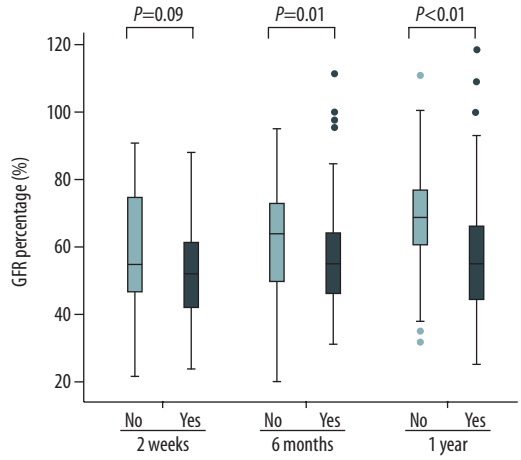


**Figure 3.** Postoperative glomerular filtration rate (GFR) percentage classified by perioperative ketorolac use. GFR percentage at 6 months and 1 year after living donor nephrectomy was significantly lower in the ketorolac group than in the non-ketorolac group.

This result is important in that ketorolac is still used in many transplant centers in the USA, and our result shows a possible risk for kidney donors to develop CKD.

Inadequate postsurgical pain control leads to delayed hospital discharge, unanticipated readmission, delayed convalescence, and increased health care costs [14]. Pain management by far remains opioid-based; this has adverse drug events, including postoperative ileus and respiratory depression [15]. The advantage of NSAIDs for postoperative pain is that they have fewer potentially significant adverse effects compared to traditional narcotic medications [6,16,17]. Ketorolac is indicated for short-term management for postoperative pain [5,18] and its potency and efficacy are comparable to that of opioids and steroidal drugs [18]. The addition of ketorolac to the narcotic enables better pain control than narcotic alone, and



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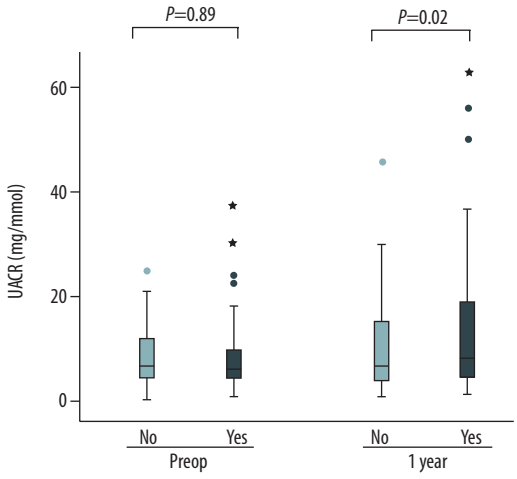


**Figure 4.** Urinary albumin/creatinine ratio (UACR) classified by perioperative ketorolac use. UACR at 1 year after living donor nephrectomy was significantly higher in the ketorolac group than in the non-ketorolac group.

ketorolac decreases the need for narcotics by up to 50% [19]. Breda et al. found that with implementation of a strict bowel preparation regimen and the use of ketorolac for postoperative analgesia, the donor length of stay was markedly reduced [9]. In our study, LOS was significantly shorter with ketorolac use. Perioperative ketorolac use showed significant decrease in pain scores at 24 h, and its intraoperative use also showed significant pain reduction immediately after LDN. Furthermore, when patients were classified by dose used, the pain scores at 24 h were reduced in a dose-dependent manner. These results are compatible with those of previous studies.

Expediting recovery and minimizing risk of renal impairment are especially important in living kidney donors, particularly when older donors are being used. Ketorolac decreases circulating vasodilatory prostaglandins, which promote the constriction of arterial smooth muscle in the renal vasculature. This creates the potential for renal ischemia and decrease in GFR, increasing the risk of acute renal insufficiency. Previous studies have reported the safety of ketorolac administration after LDN. Short-term ketorolac use shows a slight, transient, but clinically unimportant, reduction in CR clearance or showed no effect at all. Freedman et al. found that patients who received ketorolac showed slightly lower CR clearance 2 days after LDN, but CR clearance did not differ at 3 months [8]. Grimsby et al. conducted a randomized clinical trial of a continuous infusion of ketorolac *vs.* placebo after LDN and found no statistically significant change in serum CR levels on postoperative day 1 [20]. On the other hand, a few studies have evaluated the long-term renal function of ketorolac after renal donation [11,12]. In our

**Table 3.** Univariate and multivariate analyses for GFR <49% 1 year after LDN (N=47/191 cases).

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | CI | *P* | OR | CI | *P* |
| Age ≥50 | 1.57 | 0.76–3.00 | 0.24 | – | – | – |
| Gender, Female | 2.27 | 1.07–4.82 | 0.03 | 3.02 | 1.31–6.99 | 0.01 |
| Ethnicity, non-African American | 0.93 | 0.39–2.26 | 0.88 | – | – | – |
| Smoking within 6 months prior to LDN, yes | 1.15 | 0.45–2.98 | 0.77 | – | – | – |
| Preoperative comorbidity | | | | | | |
| Hypertension, yes | 2.63 | 0.92–7.49 | 0.07 | 4.72 | 1.46–15.26 | 0.01 |
| Hyperlipidemia, yes | 0.29 | 0.036–2.34 | 0.25 | – | – | – |
| BMI (kg/m$^2$) ≥30 | 1.031 | 0.51–2.09 | 0.93 | – | – | – |
| Side of LDN, left | 1.31 | 0.14–12.06 | 0.81 | – | – | – |
| Remnant kidney size (per 1.0 cm up) | 1.10 | 0.79–1.57 | 0.56 | – | – | – |
| Intraoperative lowest MAP <60 mmHg, yes | 2.86 | 1.10–7.42 | 0.03 | 3.42 | 1.22–9.55 | 0.02 |
| Operative time (per 1 min up) | 1.00 | 0.99–1.01 | 0.53 | – | – | – |
| Estimated blood loss (per 1 ml up) | 0.99 | 0.99–1.00 | 0.74 | – | – | – |
| Ketolorac use (per 15 mg up) | 1.30 | 1.11–1.52 | 0.001 | 1.38 | 1.14–1.60 | 0.001 |
| Intraoperative ketorolac use, yes | 0.65 | 0.32–1.31 | 0.23 | – | – | – |
| SBP 140 mm Hg at 1 year after LDN, yes | 1.22 | 0.22–6.42 | 0.83 | – | – | – |

GFR – glomerular filtration rate; LDN – living donor nephrectomy; OR – odds ratio; CI – confidence interval; BMI – body mass index; MAP – mean arterial pressure; SBP – systolic blood pressure.



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study, ketorolac caused significant GFR reduction 1 year after LDN, which can be attributed to slow recovery of kidney function after ketorolac use.

The normal range of UACR has been conventionally considered to be less than 30 mg/g [21]. However, recent studies have demonstrated UACR greater than 10 mg/g was associated with an increased risk of CKD [22] and all-cause and cardiovascular mortality [23]. Regarding living donors, Yoon et al. found that patients with delayed renal function recovery after LDN had higher UACR than in the normal renal function recovery group [24]. In our study, UACR 1 year after LDN was significantly higher with perioperative use of ketorolac. Its level was greater than 10 mg/g (12.6 mg/g), which suggests potential risk of CKD. Furthermore, ketorolac use was a risk factor for GFR reduction after LDN, and perioperative use of even 1 dose of ketorolac (15 mg) caused approximately 1.4 times higher risk of GFR reduction at 1 year. The results of the present study indicate that the median-use dose of 45 mg results in approximately 3 times higher chance of GFR reduction more than 50% at 1 year after LDN. Or results suggest that using ketorolac perioperatively can impair kidney function in the long term and can be a risk of CKD.

We acknowledge limitations of our study. First, the data are retrospective in nature, with a small number of patients. Second, we could not assess several postoperative confounders which can affect renal function. For example, data regarding use of postoperative over-the-counter NSAIDS and smoking status after discharge are missing. Despite these limitations, we emphasize that this is the first study to describe the risk associated with ketorolac use after LDN. Prospective clinical trials are needed to reassess its safety.

## Conclusions

Our results suggest that ketorolac is a long-term risk factor for renal dysfunction after LDN. This is the first report indicating long-term renal impairment caused by perioperative ketorolac use after LDN.

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