Short-term Administration of Diclofenac Sodium Affects Renal Function After Laparoscopic Radical Nephrectomy in Elderly Patients

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Objective: Non-steroidal anti-inflammatory drugs decrease the glomerular filtration rate. However, few studies have been conducted on renal function in patients treated with non-steroidal anti-inflammatory drugs during the first week after laparoscopic radical nephrectomy. The purpose of this study is to determine whether short-term administration of non-steroidal anti-inflammatory drugs during the first week after laparoscopic radical nephrectomy is a risk factor for impaired renal function.

Methods: Renal carcinoma patients undergoing laparoscopic radical nephrectomy in Nagoya University Hospital from April 2004 to July 2010 were identified in a retrospective cohort study. The 164 patients were divided into non-steroidal anti-inflammatory drug-treated (n = 50) and non-steroidal anti-inflammatory drug-treated (n = 114) groups.

Results: Elderly patients (>60 years old) in the non-steroidal anti-inflammatory drug-treated group showed a significant correlation between the residual renal function ratio and the total dose of diclofenac sodium (r = 0.277, P < 0.05). There was no significant correlation between the residual renal function ratio and the total dose of loxoprofen sodium. The time to doubling of the serum creatinine level was significantly shorter in elderly patients treated with diclofenac sodium compared with that in patients treated with non-steroidal anti-inflammatory drugs (P = 0.034). These results suggest that renal ischemia induced by short-term administration of diclofenac sodium impairs renal function in elderly patients after laparoscopic radical nephrectomy.

Conclusions: In the present study, we found the first evidence that short-term administration of diclofenac sodium is one risk factor for renal impairment after laparoscopic radical nephrectomy in elderly patients. To prevent renal impairment after laparoscopic radical nephrectomy in elderly patients, the use of loxoprofen sodium, which has a negligible effect on renal function compared with diclofenac sodium, is recommended.

Key words: non-steroidal anti-inflammatory drugs – kidney failure – elderly – Japanese patients – adverse effect
INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve surgical pain. NSAIDs inhibit the synthesis of renal prostaglandins (PGs) and decrease glomerular filtration rate (GFR) (1–5). Renal impairment after laparoscopic radical nephrectomy (LRN) and open radical nephrectomy (ORN) is unavoidable in patients with chronic kidney disease (CKD).

The previous study has reported that renal cyclooxygenase (COX)-2 expression selectively increases (6) and treatment with a potent COX-1 and COX-2 inhibitor (indomethacin) or a selective COX-2 inhibitor (NS-398) partially prevents the renal functional changes (7) after renal ablation in rats. However, few studies have been conducted on renal function in patients treated with NSAIDs, COX-1 and/or COX-2 inhibitors during the first week after LRN. We have reported that in patients treated with NSAIDs, COX-1 and/or COX-2 inhibitors during the first week after LRN, the residual renal function ratios were estimated from 99m-mercaptoacetyltriglycine (MAG3) diuretic renography before operation. ERPF ratios were estimated from ERPF value as follows:

\[
\text{ERPF ratios (\%)} = \frac{\text{Healthy kidney's ERPF value}}{\text{Disease kidney's ERPF value}} \times 100
\]

PATIENTS AND METHODS

STUDY PROCEDURES

This retrospective cohort study was approved by the ethics boards of Nagoya University Hospital. In the period between April 2004 and July 2010, we identified Japanese patients with renal carcinoma who were not on dialysis, had no active nephritis and who underwent LRN at Nagoya University Hospital. The subjects were divided into non-NSAID- and NSAID-treated groups. Renal function in patients was evaluated using estimated GFR (eGFR) values, calculated by the modified IDMS-MDRD Study equation (9) as follows:

If male: eGFR (ml/min) = 194 × serum creatinine\(^{-1.094}\) × age\(^{-0.287}\) × BSA/1.73

If female: eGFR (ml/min) = 194 × serum creatinine\(^{-1.094}\) × age\(^{-0.287}\) × 0.739 × BSA/1.73

The residual renal function ratios were estimated from the eGFR value as follows: postoperative eGFR value/preoperative eGFR value × 100 = residual renal function ratio (%). The effective renal plasma flow (ERPF) of the healthy kidney of each subject was evaluated using Tc 99m-mercaptoacetyltriglycine (MAG3) diuretic renography before operation. ERPF ratios were estimated from ERPF value as follows:

Healthy kidney’s ERPF value/disease kidney’s ERPF value × 100 = ERPF ratios (%).

EVALUATED ITEMS

Preoperative characteristics of patients who were recorded were age, gender, body mass index (BMI), body surface area (BSA), the number of elderly patients, the presence of hypertension, DM, eGFR and ERPF. Postoperative characteristics that were recorded were eGFR, volume of blood loss, operation duration time and total dose of each NSAID. Hypertension was defined as treatment with antihypertensive drugs, systolic pressure >140 mmHg or diastolic pressure >90 mmHg. DM was defined as treatment with hypoglycemic drugs, fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2 h plasma glucose ≥11.1 mmol/l (200 mg/dl). Elderly patients were defined as those over 60 years old (10). To investigate the progression of CKD, which was defined as a doubling of the serum creatinine level (11), we had followed the serum creatinine level for 2 years.

STATISTICAL ANALYSIS

The Fisher exact test was used to analyze patient characteristics including gender, the number of elderly patients, the number of patients with hypertension and DM. The t-test was used to identify differences in age, BMI, BSA, pre- and postoperative eGFR values, volume of blood loss and operation duration time. The relationship between the residual renal function ratio and the total dose of each NSAID was analyzed using the Pearson correlation analysis test. We calculated the time to doubling of the serum creatinine level using the Kaplan–Meier curves. In all tests, a two-sided P value of <0.05 was considered significant.

RESULTS

CHARACTERISTICS OF SUBJECTS

One hundred and sixty-six patients with renal carcinoma, who were not on dialysis, did not have active nephritis and, who underwent LRN at Nagoya University Hospital, were identified. Two patients with low and high ERPF ratios (<60 and >167%, respectively) were excluded from the analysis because the ERPF ratio indicates the degree of healthy kidney function before LRN and the maintenance of renal function after LRN is dependent on kidney function remaining intact. The 164 renal carcinoma patients were divided into non-NSAID-treated (n = 50) and NSAID-treated (n = 114) groups. Since only 4 out of 114 patients had used flurbiprofen axetil injection and remaining patients (n = 110) had used diclofenac sodium (DF: n = 56),
loprofen sodium (LP: \(n = 28\)) and DF/LP \((n = 26)\), we focused on two drugs and analyzed 160 patients except for 4 patients, about several items (correlation analysis test).

The clinical features of the analyzed patients \((n = 160)\) are shown in Table 1. No significant differences in terms of average age, gender, BMI, BSA, pre-and post-operative eGFR values, volume of bleeding, operation duration time, the number of elderly patients, hypertensive patients and DM patients were identified between non-NSAID- and NSAID-treated groups. Total doses of DF and LP in

Table 1. Characteristics in non-NSAID- and NSAID-treated groups

<table>
<thead>
<tr>
<th></th>
<th>Non-NSAID-treated group ((n = 50))</th>
<th>NSAID-treated group ((n = 110))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.77 ± 1.81</td>
<td>57.18 ± 1.35</td>
<td>0.519</td>
</tr>
<tr>
<td>Men:women</td>
<td>34:16*</td>
<td>72:38*</td>
<td>0.739</td>
</tr>
<tr>
<td>BMI</td>
<td>22.80 ± 0.48</td>
<td>23.30 ± 0.34</td>
<td>0.410</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative eGFR</td>
<td>72.10 ± 2.55</td>
<td>73.87 ± 1.69</td>
<td>0.560</td>
</tr>
<tr>
<td>Day 0 eGFR (mL/min)</td>
<td>56.71 ± 2.26</td>
<td>57.16 ± 1.30</td>
<td>0.280</td>
</tr>
<tr>
<td>Day 1 eGFR (mL/min)</td>
<td>42.47 ± 1.92</td>
<td>45.58 ± 1.02</td>
<td>0.787</td>
</tr>
<tr>
<td>Day 2 eGFR (mL/min)</td>
<td>41.46 ± 2.94</td>
<td>44.17 ± 1.33</td>
<td>0.973</td>
</tr>
<tr>
<td>Day 4 eGFR (mL/min)</td>
<td>42.01 ± 1.91</td>
<td>45.21 ± 1.30</td>
<td>0.854</td>
</tr>
<tr>
<td>Day 7 eGFR (mL/min)</td>
<td>43.08 ± 1.82</td>
<td>45.03 ± 1.26</td>
<td>0.861</td>
</tr>
<tr>
<td>Volume of bleeding (mL/min)</td>
<td>103.12 ± 24.39</td>
<td>74.41 ± 12.44</td>
<td>0.246</td>
</tr>
<tr>
<td>Operation duration time (min)</td>
<td>247.42 ± 9.64</td>
<td>255.59 ± 4.90</td>
<td>0.403</td>
</tr>
<tr>
<td>Over 60 years old</td>
<td>29*</td>
<td>54*</td>
<td>0.301</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25*</td>
<td>48*</td>
<td>0.313</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5*</td>
<td>13*</td>
<td>1.000</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>56*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loxoprofen sodium</td>
<td>28*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac sodium/loxoprofen sodium</td>
<td>26*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of diclofenac sodium (mg)</td>
<td>46.99 ± 5.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of loxoprofen sodium (mg)</td>
<td>117.86 ± 17.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Renal function was evaluated using estimated glomerular filtration rate (eGFR) values calculated by the modified IDMS-MDRD Study equation. Each value is presented as median ± SE or number of subjects.
have also reported that short-term administration of NSAIDs does not affect renal function in DM patients (8). In the present study, for DM patients in NSAID-treated group, there was not a significant correlation between the residual renal function ratio and total doses of DF or LP, which is consistent with our previous report (8). However, there was...
weak, but a significant correlation between the residual renal function ratio and total doses of DF, but not of LP in elderly patients that underwent LRN. Interestingly, the time to doubling of the serum creatinine level was significantly shorter in elderly patients treated with DF, compared with that with non-NSAIDs. Despite DF and LP are the same COX inhibitors, the results were different. The reason for this discrepancy between DF and LP is unknown. One possible explanation is differences in the selectivity of both drugs for COX-1 and COX-2 inhibition. Since the potency of DF for COX-1 and COX-2 are 10- and 120-fold stronger, respectively, compared with those of LP (21), DF strongly inhibits only COX-2, but also COX-1 and appears to be a higher rate in a decrease in renal function than celecoxib, a selective COX-2 inhibitor (22,23). A potent COX-1 and COX-2 inhibitor as indomethacin was markedly decreased in the synthesis of vasodilatory PG in a renal ablation model than a selective COX-2 inhibitor (7). In elderly patients, renal blood flow (24,25) and urinary PGI2 excretion (26) were decreased. Taken together with these findings, short-term administration of DF is one risk factor for renal impairment after LRN in elderly patients. To prevent renal impairment after LRN in elderly patients, the use of LP, which has a negligible effect on renal function compared with DF, is recommended.

**Conflict of interest statement**

None declared.

**References**


