

Impact of Nonsteroidal Anti-Inflammatory Drug Administration for 12 Months on Renal Function

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Abstract

Background: The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of renal complications. Resolution of renal side effects following NSAID administration has been observed following short-term use. Thus, the aim of the present study was to investigate whether switching from long-term NSAID administration to tramadol hydrochloride/acetaminophen (TA) combination tablets results in reversal of renal side effects.

Methods: This was a longitudinal retrospective study of 99 patients with chronic musculoskeletal pain. The patients were administered NSAIDs daily during the first 12 months followed by daily TA combination tablets for 12 months. Estimated glomerular filtration rate (eGFR) and serum levels of aspartate aminotransferase and alanine transaminase were measured at baseline, after NSAIDs administration, and after TA administration.

Results: eGFR was significantly reduced following 12-month NSAIDs administration (median, from 84.0 mL/min/1.73 m² to 72.8 mL/min/1.73 m²), and further reduction was prevented following the subsequent 12-month TA administration. Reduction in eGFR was less in patients who received celecoxib (median, -1.8 mL/min/1.73 m²) during the first 12 months. There was no significant difference in aspartate aminotransferase and alanine transaminase in each period.

Conclusions: Thus, patients receiving NSAIDs for 12 months displayed both reversible and irreversible reduction of eGFR upon cessation of NSAIDs and switching to TA. Our data highlights the potential safety benefit of utilizing multimodal analgesic therapies to minimize the chronic administration of NSAIDs.

Background

Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) to treat chronic musculoskeletal pain has become widely used in the clinic due to their ability to provide effective levels of pain relief [1–6]. However, regular administration of NSAIDs has an increased risk of gastrointestinal, cardiovascular and renal complications [1–6]. Despite the high incidence of dose/duration-dependent renal side effects (estimated at 1–5%) [7, 8], there is a paucity of data regarding the long-term safety of NSAID therapy, and the risk of renal damage has prompted an increasing appreciation in the value of multimodal analgesia in the management of moderate-to-severe pain. For example, tramadol hydrochloride/acetaminophen (TA) combination tablets have emerged as a particularly useful option for chronic pain management [5, 6].

Previous studies have demonstrated that the renal side effects of NSAIDs are usually reversible [7, 9, 10], but such studies have several limitations. For example, Chou et al. showed the risk of kidney injury is higher in current NSAID users than in past NSAID users versus control [9], which suggests the renal risks from NSAIDs could be reversible. However, they defined past NSAID users as having a termination date of 31 to 180 days before the index date, regardless of administration period. Moreover, Shukla et al. reported that rises in kidney injury biomarkers resulting from regular NSAID therapy for spondyloarthritis are seen as early as 1 week, and continue to rise up to 6 weeks [10]. Notably, the same study also showed reversibility in the rise of kidney injury biomarkers at 12 weeks upon stopping the drug [10]. Taken together, these studies show that

regular administration of NSAIDs results in chronic renal failure [7], but patients taking NSAIDs for 6 weeks or less may have a chance of recovery [10]. Based on the potentially intolerable side effects or suboptimal pain relief, substantial proportions of musculoskeletal pain patients are often switched to a different treatment within 12 months of initiating NSAID treatment [11–13]. However, no study to date has evaluated the potential safety benefit of this common practice: reversing renal side effects following cessation of long-term NSAID therapy.

Thus, the aim of the present study was to investigate a series of patients with chronic musculoskeletal pain who underwent long-term NSAIDs administration followed by switching to TA combination tablets to study the impact of NSAID-induced renal side effects.

Methods

Subjects

The Research Ethics Committee of Amagasaki Central Hospital approved this study. Data were retrospectively collected from medical records of 602 consecutive out-patients with chronic musculoskeletal pain from July 2011 to February 2012 at a primary care clinic. Of these, 204 patients, who were administered TA combination tablets, were enrolled in the present study. Inclusion criteria included age ≥ 20 years old, pain-medication-naïve prior to initiation, and existence of chronic musculoskeletal pain over the follow-up period of 2 years. Chronic musculoskeletal pain was defined as persisting, continuous, or intermittent pain for longer than 3 months [14]. Exclusion criteria were cancer-related pain, presence of neurological signs, evidence of bone fractures, recent surgery within the past 6 months, positive pregnancy test, American Society of Anesthesiologists' physical status ≥ 3 , allergy or contraindication to the tested substances, severe kidney or liver function disorders, acute duodenal or ventricular ulcer, or laboratory data outside of normal ranges.

All patients with chronic musculoskeletal pain were routinely switching medication every 12 months [11–13]. Of these, 99 patients receiving daily NSAIDs during the first 12 months followed by receiving daily TA combination tablets for 12 months were analyzed in this study. Consistent use over the 12-month period was confirmed, and patients were included regardless of administration dose. Concomitant medications were not permitted.

The number of subjects was determined by a sample size estimation using G*Power software (v 3.0.10; Franz Faul, Kiel University, Kiel, Germany). On the basis of the effect size of 0.3, the minimum number of subjects was estimated to be 90 for an α -level of 0.05 and a power ($1 - \beta$) of 0.80.

Treatment Characteristics

NSAIDs used in the study included meloxicam, loxoprofen, diclofenac, celecoxib, and others were used. During the latter 12 month period, all study participants were administrated daily TA combination tablets (Ultracet®). Change of administration dose was permitted. The initial dosage and administration of TA was

one tablet (tramadol hydrochloride 37.5 mg and acetaminophen 325 mg) given orally four times per day [15]. The dose could be increased or decreased depending on patients' symptoms, but no more than two tablets per administration was permitted (up to a maximum of eight tablets daily). No other supplementary analgesic medications were given during the study. Discontinuation of medication for the treatment of internal comorbidities was not required.

Outcomes

Patient characteristics included age, gender, major diagnosis, comorbidities, number of medications for comorbidities, and administration dose. Laboratory values were routinely collected at baseline, after 12-month NSAID administration, and after 12-month TA administration. Comparisons of laboratory results during the 12 months with daily NSAIDs and during the following 12 months with daily administration of TA combination tablets were made in the same patient.

The primary outcome measure was serum levels of estimated glomerular filtration rate (eGFR). eGFR was calculated as follows [16]: $194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$ (if female, $\times 0.739$). The eGFR values (mL/min/1.73 m²) in a given range were stratified into one of the following published chronic kidney disease (CKD) categories [17]: grade 1, normal or high, ≥ 90 ; grade 2, mildly decreased, 60–89; grade 3a, mildly to moderately decreased, 45–59; grade 3b, moderately to severely decreased, 30–44; grade 4, severely decreased, 15–29; grade 5, kidney failure, < 15 ; or dialysis. Patients who were categorized with an increase in severity of at least one grade in CKD category were enrolled for NSAID and TA administration.

Secondary outcome measures were serum levels of aspartate transaminase (AST) and alanine Transaminase (ALT). Other information regarding adverse events during treatment were also collected.

Statistical analysis

Relative change in eGFR, AST, and ALT from baseline (x_b) and measurements was calculated using the equation $(x - x_b) / x_b$, where x is the measured value. Normality of distribution for each measurement was evaluated using the Shapiro-Wilk test for continuous variables. The outcome variables were not normally distributed, thus continuous data are expressed as medians and interquartile ranges (IQR). Categorical variables were analyzed using the chi-square test. Continuous variables were analyzed using Mann-Whitney U test, Kruskal-Wallis test, Friedman test, Steel-Dwass test, and Spearman's rank correlation coefficient test.

All data were statistically analyzed using the SPSS 25.0J program, and P values < 0.05 were considered significant.

Results

Of the 99 patients, 70 (71%) were female (Table 1). The median age was 73 years (IQR, 47–81). Major diagnoses (multiple allowed) of the patients included lumbago ($n = 45$), osteoarthritis ($n = 28$), and rheumatoid arthritis ($n = 3$). NSAIDs taken during the first 12 months included meloxicam ($n = 31$), loxoprofen

(n = 25), diclofenac (n = 13), and celecoxib (n = 20). No significant difference in patient characteristics was observed based on the particular NSAID used. The median administration dose of NSAIDs was 75 mg per day (IQR, 10–180), and the median administration dose of TA was two tablets per day (IQR, 1–4). No severe complications occurred during the two-year research period.

Table 1
Patient characteristics

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|--|---------------------|-----------------------|------------------------|------------------------|-----------------------|-------------------|
| <i>Demographics</i> | | | | | | |
| Age [year] | 73 [47–81] | 68 [45–81] | 80 [59–83] | 73 [45–82] | 71 [47–80] | 77 [68–83] |
| Female, n (%) | 70 (71%) | 23 (74%) | 17 (68%) | 8 (62%) | 16 (80%) | 6 (60%) |
| <i>Major diagnoses (multiple allowed)</i> | | | | | | |
| Lumbago, n (%) | 45 (45%) | 11 (35%) | 17 (68%) | 5 (38%) | 8 (40%) | 4 (40%) |
| Osteoarthritis, n (%) | 28 (28%) | 7 (23%) | 4 (16%) | 4 (31%) | 9 (45%) | 4 (40%) |
| Rheumatoid arthritis, n (%) | 3 (3%) | 3 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| <i>Comorbidities</i> | | | | | | |
| Diabetes, n (%) | 4 (4%) | 0 (0%) | 2 (8%) | 1 (8%) | 0 (0%) | 1 (10%) |
| Hypertension, n (%) | 22 (22%) | 4 (13%) | 9 (36%) | 4 (31%) | 3 (15%) | 2 (20%) |
| Chronic heart failure, n (%) | 3 (3%) | 0 (0%) | 2 (8%) | 0 (0%) | 1 (5%) | 0 (0%) |
| Dyslipidemia, n (%) | 1 (1%) | 0 (0%) | 1 (4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hypothyroidism, n (%) | 2 (2%) | 2 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Osteoporosis, n (%) | 5 (5%) | 2 (6%) | 1 (4%) | 0 (0%) | 2 (10%) | 0 (0%) |
| Migraine, n (%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (10%) |
| Depression, n (%) | 2 (2%) | 0 (0%) | 1 (4%) | 0 (0%) | 0 (0%) | 1 (10%) |
| Number of medications for comorbidities, n (%) | | | | | | |
| 0 | 61 (62%) | 21 (68%) | 11 (44%) | 9 (69%) | 14 (70%) | 6 (60%) |
| 1 | 24 (24%) | 9 (29%) | 9 (36%) | 1 (8%) | 4 (20%) | 1 (10%) |
| 2 | 9 (9%) | 1 (3%) | 4 (16%) | 1 (8%) | 2 (10%) | 1 (10%) |
| 3 | 3 (3%) | 0 (0%) | 1 (4%) | 1 (8%) | 0 (0%) | 1 (10%) |
| 4 | 2 (2%) | 0 (0%) | 0 (0%) | 1 (8%) | 0 (0%) | 1 (10%) |

NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen

Data of sex, major diagnoses, and comorbidities are number and (%) of patients. Data of age, and administration dose are medians and interquartile ranges [IQR].

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|--|---------------------|-----------------------|------------------------|------------------------|-----------------------|-------------------|
| <i>Administration dose per day</i> | | | | | | |
| NSAIDs [mg] | 75 [10–180] | 10 [10–10] | 180 [75–180] | 62.5 [75–110] | 200 [200–200] | 62.5 [12–450] |
| TA [tablets] | 2 [1–4] | 3 [2–4] | 2 [1–3] | 2 [2–4] | 2 [1–4] | 2 [1–3] |
| NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen | | | | | | |
| Data of sex, major diagnoses, and comorbidities are number and (%) of patients. Data of age, and administration dose are medians and interquartile ranges [IQR]. | | | | | | |

The median baseline for eGFR was 84.0 mL/min/1.73 m² (IQR, 67.6–102.0), the median baseline for AST was 20.0 U/L (IQR, 17.0–24.0), and the median baseline for ALT was 16.0 U/L (IQR, 11.0–22.0) (Table 2). eGFR level was significantly correlated with age at baseline ($r = -0.606$), after NSAIDs administration for 12 months ($r = -0.682$), and after TA administration for 12 months ($r = -0.645$). Greater reduction of eGFR showed a tendency to associate with advanced age during the NSAID administration period ($r = -0.179$, $p = 0.077$), but not with age during the subsequent 12 months with TA administration. In addition, the change in eGFR levels during the first 12 months with NSAID administration was significantly different between patients with diabetes mellitus (median, -28.3 mL/min/1.73 m²; $n = 4$) and those without diabetes mellitus (-10.9 mL/min/1.73 m²; $n = 95$) ($p = 0.043$), whereas there was no significant difference found during the subsequent 12-month TA administration.

Table 2
Course of laboratory levels

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|--|----------------------|-----------------------|------------------------|------------------------|-----------------------|--------------------|
| <i>eGFR</i> [mL/min/1.73 m ²] | | | | | | |
| Baseline | 84.0 [67.6–102.0] | 86.0 [75.7–104.0] | 84.0 [65.1–93.8] | 92.1 [65.0–116.5] | 83.1 [57.1–98.1] | 74.6 [64.3–88.3] |
| After NSAIDs for 12 months | 72.8 [57.5–89.6]* | 73.8 [60.9–89.6]* | 72.1 [49.3–92.2] | 72.6 [48.2–85.7] | 76.2 [61.4–90.5] | 66.7 [50.8–75.5] |
| After TA for 12 months | 71.5 [57.7–88.7]* | 72.9 [64.1–92.7]* | 71.7 [53.7–90.4] | 71.3 [56.2–97.5] | 75.3 [58.0–84.5] | 57.5 [43.8–77.3] |
| Changes during NSAIDs use | -13.8 [-25.0–0.0] | -18.8 [-28.7–-5.9]† | -2.7 [-19.3–0.0] | -21.5 [-31.2–-12.5]† | -1.8 [-14.1–0.0] | -14.8 [-27.6–-5.8] |
| Changes during TA use | 0.4 [-7.5–11.8] | 4.0 [-7.5–14.0] | 1.9 [-6.6–13.5] | 1.5 [-1.1–15.0] | -2.8 [-9.9–11.0] | -8.5 [18.6–8.7] |
| <i>AST [U/L]</i> | | | | | | |
| Baseline | 20.0 [17.0–24.0] | 20.0 [17.0–22.0] | 22.0 [18.5–26.5] | 21.0 [15.5–30.0] | 19.0 [16.0–28.8] | 22.5 [15.0–25.3] |
| After NSAIDs for 12 months | 21.0 [16.0–25.0] | 21.0 [16.0–24.0] | 22.0 [16.5–26.0] | 18.0 [15.5–21.0] | 23.0 [15.0–31.0] | 20.0 [16.5–22.5] |
| After TA for 12 months | 19.0 [16.0–24.0] | 19.0 [16.0–22.0] | 22.0 [19.0–27.0] | 18.0 [15.0–21.5] | 19.5 [17.0–28.0] | 17.0 [15.8–21.8] |
| Changes during NSAIDs use | 0.0 [-12.5–17.6] | 5.0 [-6.3–17.6] | -4.3 [-15.0–16.3] | -4.5 [-22.8–6.7] | 1.6 [-16.9–18.5] | 0.0 [-18.2–19.1] |
| Changes during TA use | -5.6 [-17.1–5.9] | -6.7 [-20.0–4.8] | 0.0 [-7.7–14.4] | -5.3 [-14.8–0.0] | -10.2 [-16.6–6.5] | -16.7 [-20.0–3.3] |

eGFR, estimated Glomerular Filtration Rate; AST, aspartate transaminase; ALT, alanine Transaminase; NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen

Data are medians and interquartile ranges [IQR]. These data were analyzed using Kruskal-Wallis test and Steel-Dwass test. The significance level was set at less than 5%. *Significant difference versus baseline. †Significant difference versus Celecoxib. eGFR after NSAIDs for 12 months and after TA for 12 months were significantly decreased than baseline, in overall and Meloxicam.

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|---|---------------------|-----------------------|------------------------|------------------------|-----------------------|-------------------|
| <i>ALT [U/L]</i> | | | | | | |
| Baseline | 16.0 [11.0–22.0] | 15.0 [11.0–20.0] | 17.0 [11.0–27.5] | 15.0 [10.5–29.5] | 17.5 [10.3–23.5] | 16.5 [10.0–25.0] |
| After NSAIDs for 12 months | 15.0 [10.0–21.0] | 14.0 [10.0–19.0] | 16.0 [9.0–28.5] | 12.0 [9.0–24.5] | 15.0 [11.0–25.0] | 15.0 [10.5–20.3] |
| After TA for 12 months | 14.0 [10.0–21.0] | 12.0 [9.0–16.0] | 17.0 [12.0–23.0] | 12.0 [8.0–19.5] | 14.5 [11.0–25.8] | 13.5 [10.0–21.0] |
| Changes during NSAIDs use | 0.0 [-25.0–23.5] | 8.3 [-20.0–23.5] | -10.0 [-38.7–17.7] | -10.0 [-33.9–-1.8] | 6.5 [-29.6–37.2] | -9.2 [-25.3–19.8] |
| Changes during TA use | -9.1 [-27.6–8.3] | -11.1 [-40.0–7.7] | 0.0 [-26.1–20.8] | -12.5 [-28.1–17.8] | -8.1 [-27.3–8.4] | -10.1 [-34.2–5.0] |
| eGFR, estimated Glomerular Filtration Rate; AST, aspartate transaminase; ALT, alanine Transaminase; NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen | | | | | | |
| Data are medians and interquartile ranges [IQR]. These data were analyzed using Kruskal-Wallis test and Steel-Dwass test. The significance level was set at less than 5%. *Significant difference versus baseline. †Significant difference versus Celecoxib. eGFR after NSAIDs for 12 months and after TA for 12 months were significantly decreased than baseline, in overall and Meloxicam. | | | | | | |

As shown in Table 2 and Fig. 1, eGFR levels after NSAID administration for 12 months followed by TA for 12 months were significantly reduced compared to baseline. eGFR was significantly reduced during the first 12 months with NSAIDs administration (median, from 84.0 mL/min/1.73 m² to 72.8 mL/min/1.73 m²), whereas the reduction was prevented during the following 12 months with TA administration (median, 71.5 mL/min/1.73 m²). Some patients showed an increase of eGFR following cessation of NSAIDs and switching to TA. There was no significant difference in eGFR between after the 12-month NSAIDs period and after the 12-month TA period. With respect to the four specific NSAIDs, reduction of eGFR was significantly less in patients taking celecoxib (median, -1.8 mL/min/1.73 m²) than those on meloxicam or diclofenac (Fig. 2). As shown in Table 2, Fig. 3, and Fig. 4, there was no significant difference in AST or ALT in each period.

Table 3 shows the number of patients for each grade of CKD category. Of the 99 patients, 37 patients (37%) experienced an increase in severity of at least one grade in CKD category during the first 12 months with NSAID administration. Interestingly, the extent of severity varied by NSAID type, where 15% of patients on celecoxib (n = 3) were affected, compared to 77% of patients on diclofenac (n = 10) (p = 0.003). On the other hand, during the 24 months with NSAID and TA administration, 35 patients (35%) increased severity by at least one grade of CKD category. There were 30 patients in more than three categories after NSAIDs for 12

months, whereas 28 patients in more than three categories after TA for 12 months. The number of patients increasing severity by at least one grade of CKD category over 24 months showed no significant difference among the four specific NSAIDs used. The variables other than NSAID type were not significant difference between patients with fell into at least worse one grade of CKD category or not (Table 4).

Table 3
The number of patients each grade of CKD category

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|--|-----------------------------|-------------------------------|--------------------------------|--------------------------------|-------------------------------|---------------------------|
| <i>Baseline, n (%)</i> | | | | | | |
| 1 | 38 (38%) | 13 (42%) | 8 (32%) | 8 (62%) | 7 (35%) | 2 (20%) |
| 2 | 43 (43%) | 16 (52%) | 12 (48%) | 2 (15%) | 7 (35%) | 6 (60%) |
| 3a | 13 (13%) | 1 (3%) | 3 (12%) | 3 (23%) | 5 (25%) | 1 (10%) |
| 3b | 5 (5%) | 1 (3%) | 2 (8%) | 0 (0%) | 1 (5%) | 1 (10%) |
| 4 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| <i>After NSAIDs for 12 months, n (%)</i> | | | | | | |
| 1 | 23 (23%) | 7 (23%) | 8 (32%) | 2 (15%) | 5 (25%) | 1 (10%) |
| 2 | 46 (46%) | 17 (55%) | 7 (28%) | 6 (46%) | 11 (55%) | 5 (50%) |
| 3a | 19 (19%) | 5 (16%) | 5 (20%) | 3 (23%) | 3 (15%) | 3 (30%) |
| 3b | 9 (9%) | 2 (6%) | 4 (16%) | 2 (15%) | 1 (5%) | 0 (0%) |
| 4 | 2 (2%) | 0 (0%) | 1 (4%) | 0 (0%) | 0 (0%) | 1 (10%) |
| 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| <i>After TA for 12 months, n (%)</i> | | | | | | |
| 1 | 22 (22%) | 8 (26%) | 6 (24%) | 3 (23%) | 4 (20%) | 1 (10%) |

NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen; CKD, chronic kidney disease

Data are number and (%) of patients. Of 99 patients, 37 patients (37%) experienced an increase in severity of at least one grade in CKD category during the first 12 months with NSAID administration. On the other hand, during 24 months with NSAIDs and TA administration, 35 patients (35%) increased severity by at least one grade of CKD category. These data were analyzed using chi-square test. The significance level was set at less than 5%. *Significant less number of patients. †Significant high number of patients.

| | Overall (n = 99) | Meloxicam (n = 31) | Loxoprofen (n = 25) | Diclofenac (n = 13) | Celecoxib (n = 20) | Other (n = 10) |
|---|---------------------|-----------------------|------------------------|------------------------|-----------------------|-------------------|
| 2 | 49 (49%) | 18 (58%) | 12 (48%) | 5 (38%) | 11 (55%) | 3 (30%) |
| 3a | 16 (16%) | 3 (10%) | 2 (8%) | 4 (31%) | 4 (20%) | 3 (30%) |
| 3b | 9 (9%) | 1 (3%) | 4 (16%) | 0 (0%) | 1 (5%) | 3 (30%) |
| 4 | 3 (3%) | 1 (3%) | 1 (4%) | 1 (3%) | 0 (0%) | 0 (0%) |
| 5 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| <i>Fell into at least worse one grade of CKD category, n (%)</i> | | | | | | |
| during NSAIDs use (12 months) | 37 (37%) | 13 (42%) | 7 (28%) | 10 (77%)† | 3 (15%)* | 4 (40%) |
| during NSAIDs and TA use (24 months) | 35 (35%) | 11 (35%) | 7 (28%) | 8 (62%) | 4 (20%) | 5 (50%) |
| NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen; CKD, chronic kidney disease | | | | | | |
| Data are number and (%) of patients. Of 99 patients, 37 patients (37%) experienced an increase in severity of at least one grade in CKD category during the first 12 months with NSAID administration. On the other hand, during 24 months with NSAIDs and TA administration, 35 patients (35%) increased severity by at least one grade of CKD category. These data were analyzed using chi-square test. The significance level was set at less than 5%. *Significant less number of patients. †Significant high number of patients. | | | | | | |

Table 4
Comparison between patients with fell into at least worse one grade of CKD category or not

| | During NSAIDs use (12 months) | | During NSAIDs and TA use (24 months) | |
|---|----------------------------------|-------------------------------|---|-------------------------------|
| | Fell category (n = 37) | Not fell category (n = 62) | Fell category (n = 35) | Not fell category (n = 64) |
| <i>Demographics</i> | | | | |
| Age [year] | 76 [61–84] | 72 [47–80] | 73 [60–83] | 73 [46–80] |
| Female, n (%) | 11 (30%) | 18 (29%) | 12 (34%) | 17 (27%) |
| <i>Major diagnoses (multiple allowed)</i> | | | | |
| Lumbago, n (%) | 21 (57%) | 24 (39%) | 18 (51%) | 27 (42%) |
| Osteoarthritis, n (%) | 7 (19%) | 21 (34%) | 9 (26%) | 19 (30%) |
| Rheumatoid arthritis, n (%) | 1 (3%) | 2 (3%) | 1 (3%) | 2 (3%) |
| <i>Comorbidities</i> | | | | |
| Diabetes, n (%) | 3 (8%) | 1 (2%) | 2 (6%) | 2 (3%) |
| Hypertension, n (%) | 11 (30%) | 11 (18%) | 8 (23%) | 14 (22%) |
| Chronic heart failure, n (%) | 2 (5%) | 1 (2%) | 2 (6%) | 1 (2%) |
| Dyslipidemia, n (%) | 1 (3%) | 0 (0%) | 0 (0%) | 1 (2%) |
| Hypothyroidism, n (%) | 0 (0%) | 2 (3%) | 0 (0%) | 2 (3%) |
| Osteoporosis, n (%) | 1 (3%) | 4 (6%) | 1 (3%) | 4 (6%) |
| Migraine, n (%) | 0 (0%) | 1 (2%) | 0 (0%) | 1 (2%) |
| Depression, n (%) | 1 (3%) | 1 (2%) | 1 (3%) | 1 (2%) |
| Number of medications for comorbidities | | | | |
| 0, n (%) | 21 (57%) | 40 (65%) | 23 (66%) | 38 (59%) |
| 1, n (%) | 9 (24%) | 15 (24%) | 6 (17%) | 18 (28%) |

NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen; CKD, chronic kidney disease

Data of sex, major diagnoses, and comorbidities are number and (%) of patients. Data of age, and administration dose are medians and interquartile ranges [IQR]. Of 99 patients, 37 patients (37%) experienced an increase in severity of at least one grade in CKD category during the first 12 months with NSAID administration. On the other hand, during 24 months with NSAIDs and TA administration, 35 patients (35%) increased severity by at least one grade of CKD category. These data were analyzed using chi-square test or Mann-Whitney U test. The significance level was set at less than 5%. *Significant less number of patients. †Significant high number of patients.

| | During NSAIDs use (12 months) | | During NSAIDs and TA use (24 months) | |
|--|----------------------------------|--------------|---|--------------|
| 2, n (%) | 4 (11%) | 5 (8%) | 4 (11%) | 5 (8%) |
| 3, n (%) | 1 (3%) | 2 (3%) | 1 (3%) | 2 (3%) |
| 4, n (%) | 2 (5%) | 0 (0%) | 1 (3%) | 1 (2%) |
| <i>Type of NSAIDs</i> | | | | |
| Meloxicam, n (%) | 13 (35%) | 18 (29%) | 11 (31%) | 20 (31%) |
| Loxoprofen, n (%) | 7 (19%) | 18 (29%) | 7 (20%) | 18 (28%) |
| Diclofenac, n (%) | 10 (27%)† | 3 (5%)* | 8 (23%) | 5 (8%) |
| Celecoxib, n (%) | 3 (8%)* | 17 (27%)† | 4 (11%) | 16 (25%) |
| Other, n (%) | 4 (11%) | 6 (10%) | 5 (14%) | 5 (8%) |
| <i>Administration dose per day</i> | | | | |
| NSAIDs [mg] | 75 [10–150] | 160 [10–200] | 75 [10–180] | 100 [10–180] |
| TA [tablets] | 2 [1–4] | 2 [1–3] | 2 [1–4] | 2 [1–4] |
| NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen; CKD, chronic kidney disease | | | | |
| Data of sex, major diagnoses, and comorbidities are number and (%) of patients. Data of age, and administration dose are medians and interquartile ranges [IQR]. Of 99 patients, 37 patients (37%) experienced an increase in severity of at least one grade in CKD category during the first 12 months with NSAID administration. On the other hand, during 24 months with NSAIDs and TA administration, 35 patients (35%) increased severity by at least one grade of CKD category. These data were analyzed using chi-square test or Mann-Whitney U test. The significance level was set at less than 5%. *Significant less number of patients. †Significant high number of patients. | | | | |

Discussion

The present study showed NSAID administration for 12 months significantly reduced serum levels of eGFR. However, further reduction was prevented following 12 months of TA administration. Several patients showed an increase of eGFR upon cessation of NSAIDs followed by switching to TA.

Most forms of acute renal failure from NSAIDs administration are short term and reversible upon NSAIDs discontinuation [7]. The side effects of NSAIDs are the consequences of inhibiting prostaglandin synthesis and can result in acute renal failure. Moreover, there is the possibility that chronic administration of any NSAIDs can cause chronic renal failure in some patients despite previous data suggesting it is safe [7, 18]. The underlying pathology of chronicity is considered as chronic papillary necrosis or chronic interstitial nephritis [19]. NSAIDs administration for short term for up to 6 weeks may preserve the chance for recovery [10]; however, there has previously been no study to test the reversibility of renal side effects following long-

term NSAID use. To our knowledge, the present study is the first to show the possibility of reversing renal side effects after taking NSAIDs for 12 months.

The risk profiles of side effects are different for every NSAIDs [20, 21]. In a meta-analysis of 114 clinical trials, Zhang et al. showed that rofecoxib intensified the risk for renal side effects. By contrast, among NSAIDs, celecoxib had a low risk for renal side effects [20]. Other NSAIDs were not significantly associated with the risk, although some trends were evident. Similarly, Winkelmayer et al. showed rofecoxib, ibuprofen, and indomethacin were associated with a higher risk of acute kidney injury than celecoxib [21]. In the present study, the reduction of renal function following administration of NSAIDs for 12 months tended to be less in patients receiving celecoxib compared with patients receiving other NSAIDs.

TA combination tablets, which combine tramadol hydrochloride and acetaminophen, are a widely used analgesic [22]. Tramadol is a synthetic opioid receptor agonist with analgesic properties that also has a unique monoaminergic action through serotonin-noradrenaline reuptake inhibition [23]. Acetaminophen is one of the more traditional and better-tolerated among fast-acting analgesics that block pain through different pathways than opioids [24]. The effectiveness of TA in the treatment of chronic non-cancer pain is clinically acceptable, and improvements in pain contribute to improvements in quality of life in practice [15]. Most of the side effects of TA are non-serious [15, 25–27]; it is suggested that liver enzymes are elevated in the presence of acetaminophen at doses higher than normal therapeutic levels [28]. In addition, previous work showed concomitant treatment with opioids does not lead to an elevation of liver enzyme levels [28]. Similarly, in our study we did not observe any significant elevations in liver enzymes.

There are several limitations in the present study. First, the present study is a retrospective study limited only to patients receiving daily NSAIDs during the first 12 months followed by 12 months of administration of TA combination tablets daily. There is no group receiving only daily NSAIDs or TA combination tablets during the 24 month periods. In addition, many patients had concomitant medications. Thus, our observations must be interpreted with caution. Second, the administration protocol was variable, and the overall impact of administration dose on serum levels was not determined. Third, patients were mostly of advanced age in the present study. Higher age is typically associated with greater reduction of eGFR during the first 12 months of NSAID administration. Thus, the reduction of eGFR could be overestimated. Finally, we included only a small number of participants treated at a single medical center. Further studies that investigate larger patient cohorts and additional treatment regimens are required to clarify the effects of long-term use of NSAIDs on serum levels.

Conclusions

The present study suggests that patients who have undergone long-term NSAID therapy for 12 months can experience reversible or irreversible renal damage following the cessation of NSAIDs and switching to TA, as determined by measuring eGFR. Given this risk identified in our current series of patients, our data highlights the potential safety of utilizing multimodal analgesic therapies to minimize the chronic administration of NSAIDs wherever possible.

List Of Abbreviations

NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AST, aspartate transaminase; ALT, alanine transaminase; IQR, interquartile ranges.

Declarations

Ethics approval and consent to participate

The Research Ethics Committee of Amagasaki Central Hospital approved this study. All patients have provided informed consent for the present study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

There was no funding received for this study.

Authors' contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Figures

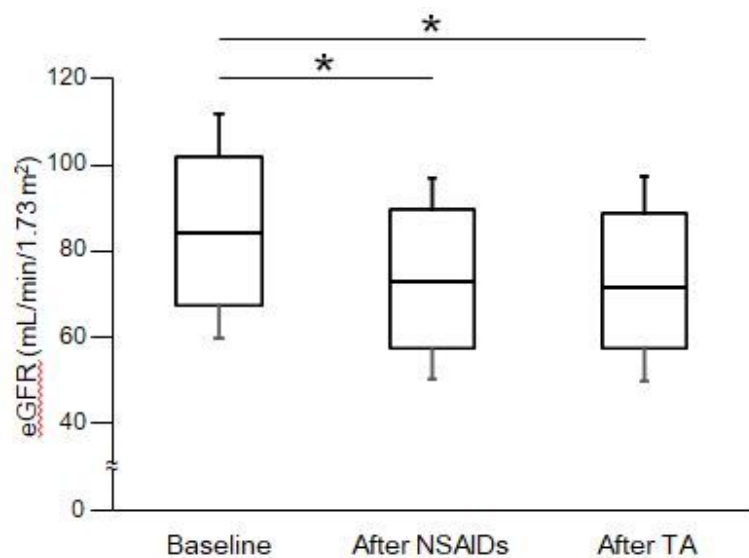


Figure 1

Course of eGFR eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen

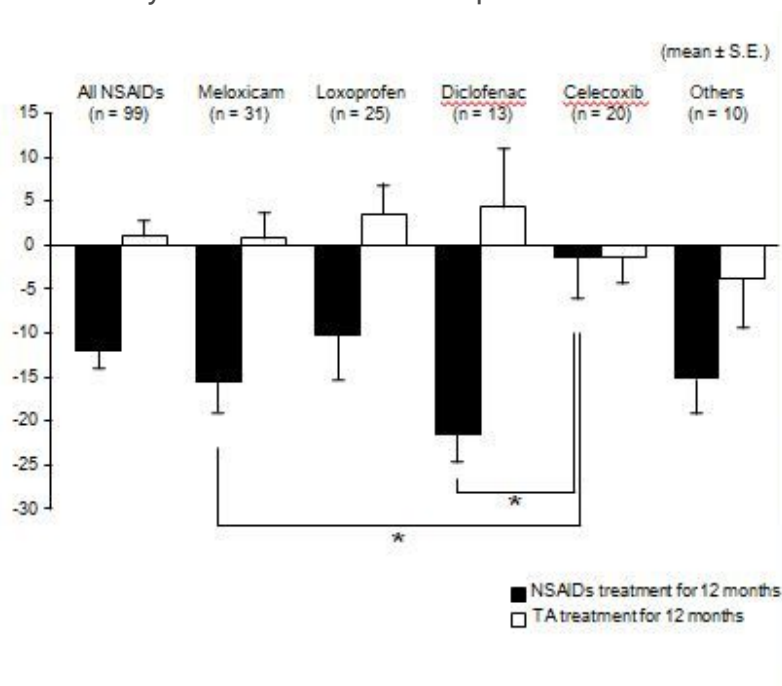


Figure 2

Course of eGFR among specific NSAIDs eGFR, estimated glomerular filtration rate; TA, tramadol hydrochloride/acetaminophen Values are means of change of eGFR and the error bar shows standard error. The reduction of eGFR was significantly lesser in patients with celecoxib than those with meloxicam and diclofenac. These data were analyzed using Kruskal-Wallis test and Steel-Dwass test. The significance level was set at less than 5%. *Significant difference among specific NSAIDs

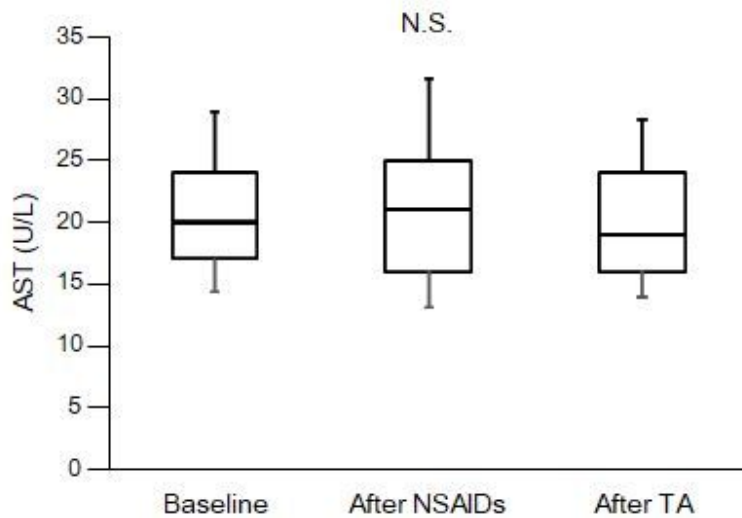


Figure 3

AST, aspartate transaminase; NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen Each box plot represents the 75 percentile, median, and 25 percentile. Error bar shows standard deviation. There was no significant difference among each period. These data were analyzed using Friedman test and Steel-Dwass test. The significance level was set at less than 5%.

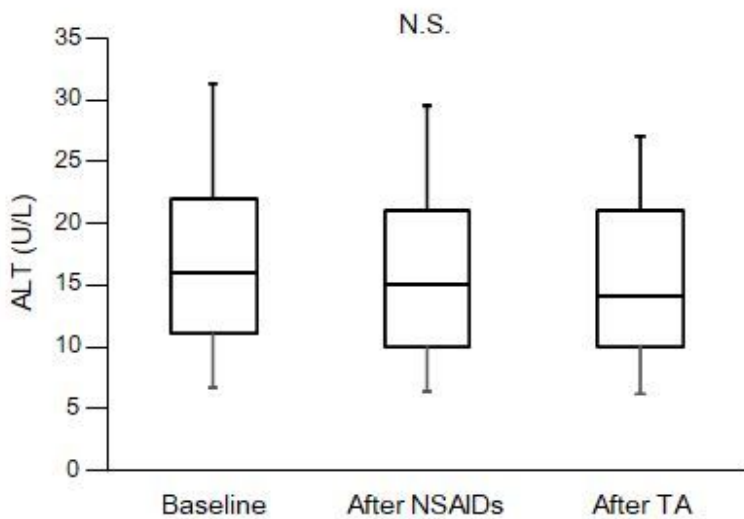


Figure 4

ALT, alanine transaminase; NSAIDs, nonsteroidal anti-inflammatory drugs; TA, tramadol hydrochloride/acetaminophen Each box plot represents the 75 percentile, median, and 25 percentile. Error bar shows standard deviation. There was no significant difference among each period. These data were analyzed using Friedman test and Steel-Dwass test. The significance level was set at less than 5%.