Renal Dysfunction with Use of Nonsteroidal Anti-Inflammatory Drugs in Patients with Cirrhosis

Yuan Liu
Pacific University
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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been known to cause renal dysfunction in healthy patients and more pronounced renal effects in patients with cirrhosis and ascites. The use of NSAIDs have been associated with hepatorenal syndrome, a serious and often fatal complication associated with acute decline in renal function in the context of cirrhosis. However, renal safety of selective cyclo-oxygenase-2 (COX-2) and non-selective COX inhibitors has not been well delineated in current research with regards to patients with cirrhosis. This literature review seeks to compare the renal safety of selective and non-selective COX inhibitors in patients with cirrhosis.

Methods: A thorough multi-database search was conducted using various combinations of keywords. Each study was evaluated using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) system.

Results: Selective COX-2 inhibitor did not produce statistically significant decrements in renal function, whereas short-term use of non-selective COX inhibitors (or NSAIDs) produced significant decreases in GFR, creatinine clearance, prostaglandin E2 levels, platelet aggregation and concurrent furosemide diuresis. However, these adverse renal effects are also largely reversible upon cessation of NSAID use.

Conclusion: Selective COX-2 inhibitors comparatively caused less renal dysfunction and interference with platelet function and diuretic therapy than non-selective COX inhibitors and may be safer in patients with cirrhosis.

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First Advisor
Annjanette Sommers, PA-C

Keywords
Renal dysfunction, renal failure, NSAID, COX inhibitor, celecoxib, ibuprofen, naproxen, sulindac, cirrhosis, ascites, liver dysfunction

Subject Categories
Medicine and Health Sciences

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Yuan Liu

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
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Faculty Advisor: Annjanette Sommers, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Yuan (Courtney) Liu was born in Nanning, China, and immigrated to Los Angeles, CA at the age of eleven. She completed her undergraduate education at the University of California at Berkeley in Molecular and Cell Biology and Integrative Biology. After working part-time as a medical assistant in an internal medicine clinic and receiving exceptional care from a physician assistant in an emergency room, she decides to pursue a career in medicine as a physician assistant. She plans to practice internal medicine for a number of years and have her first dog after obtaining a job.
Abstract

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**Keywords:** Renal dysfunction, renal failure, NSAID, COX inhibitor, celecoxib, ibuprofen, naproxen, sulindac, cirrhosis, ascites, liver dysfunction
Acknowledgements

To *my grandfather*, You taught me to have compassion, sensibility, and a sense of justice. Thank you for nourishing my young mind and continuing to influence me into adulthood.
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Table 4: Characteristics of reviewed studies, GRADE profile of studies involving use of non-selective COX inhibitors in cirrhosis
List of Abbreviations

Nonsteroidal anti-inflammatory drugs ............................................................. NSAIDs
Cyclo-oxygenase ......................................................................................... COX
Hepatorenal syndrome ................................................................................ HRS
Grading of Recommendations, Assessments, Development and Evaluation ........GRADE
Glomerular filtration rate ............................................................................ GFR
Prostaglandin ............................................................................................... PG
Renal plasma flow ......................................................................................... RPF
Platelet aggregation ....................................................................................... PA
Randomized controlled trial ........................................................................ RTC
Quasi experimental study .......................................................................... QES
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BACKGROUND

Anti-inflammatory and analgesic use in patients with cirrhosis have been challenging clinically. Currently no guidelines have been established on pain management in patients with liver dysfunction and cirrhosis. The analgesic of choice is acetaminophen at reduced maximum daily dose of 2-3 g/day, however acetaminophen does not address anti-inflammatory needs.\(^1\) On the other hand, non-steroidal anti-inflammatory drugs (NSAIDS) is less safe due to concerns of causing renal dysfunction or more severely, hepatorenal syndrome (HRS), through inhibition of production of renal-protective prostaglandins. Hepatorenal syndrome is a serious, albeit preventable and reversible complication of cirrhosis, characterized by renal dysfunction in advanced hepatic fibrosis, and often precipitated by conditions that impair renal function, such as NSAID use, dehydration, hypovolemia, or bacterial infections. Adverse drug reactions affecting renal derangements are especially pronounced in patients with cirrhosis and ascites.\(^2\text{-}^4\) Hepatorenal syndrome can be rapidly progressive, highly fatal (type 1), or may present with relatively more stable clinical conditions and longer survival (type 2).\(^3\) The etiology behind renal dysfunction in cirrhosis mainly involves vasoconstriction of renal arteries, commonly associated with use of ibuprofen, indomethacin, naproxen, sulindac and lysine-acetylsalicylate. Vasoconstriction of renal arteries, from the inhibition of vasodilating prostaglandins, decreases perfusion to the kidneys and, as a result, also decreases the glomerular filtration rate (GFR).\(^2\text{-}^5\)

Current literature is ambivalent about the renal effects of COX-2 inhibitors, whereas renal impairments from non-selective COX inhibitors have been well described.\(^6\text{-}^{10}\) Some results suggested that both COX-2 inhibitors (rofecoxib, celecoxib) and a non-selective COX inhibitor
(naproxen) caused a significant decline in urinary sodium from baseline in previously healthy elderly subjects,\cite{11} whereas another study identified significant increases in serum creatinine in prerenal azotemic patients taking a non-selective COX inhibitors (ibuprofen or diclofenac) but not a COX-2 inhibitor (celecoxib).\cite{12} In addition to a question of safety to the renal system, NSAIDs have also been associated with inhibition of platelet function and interference with diuretics, both of which can lead to serious complications in cirrhosis such as esophageal variceal bleeding, ascites, and edema.\cite{13-16} See Table 1 for a list of selective and non-selective COX inhibitors. This literature review seeks to compare renal effects of selective COX-2 and non-selective COX inhibitors in the context of cirrhosis.

**METHODS**

A systematic search for relevant studies and articles was conducted using various combinations of the following keywords: “NSAID,” “COX-II inhibitor,” “non-selective COX inhibitor,” “anti-inflammatory,” “celecoxib,” “ibuprofen,” “naproxen,” “cirrhosis,” “ascites,” “liver failure,” “renal dysfunction,” “hepatorenal syndrome,” “controlled trial,” and “pain management.” Articles were identified using Medline (PubMed and Ovid), CINAHL, Web of Science, and Google Scholars. References of pertinent articles also served as sources of information, indirectly linking the search to other articles not otherwise identified using the keywords listed above. The inclusion criteria included studies investigating the use of selective COX-II and/or non-selective NSAIDs in patients with cirrhosis. Exclusion criteria included studies in animal subjects, isolated case reports, studies involving patients without liver dysfunctions, studies of patients with prior history of hepatorenal syndrome or renal
insufficiency, and articles not available in digital format and required additional payment to request through inter-institutional library system.

Each study was evaluated for quality of study design and quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which downgrades the level of evidence based on limitations, indirectness, imprecision, inconsistency, and publication bias. Based on quality of evidence, strength of recommendation is assigned to describe the impact of results, either as a strong or weak recommendation.

RESULTS

A thorough search in different databases generated a total of 31 relevant articles, with at least two keywords in the topic. A total of 6 studies met eligibility criteria and are included in this review. One study, a randomized control study, compared a selective COX-2 inhibitor, a non-selective COX inhibitor, and placebo. A pilot study only evaluated a selective COX-2 inhibitor. While, the four remaining studies measured the renal effects of non-selective COX inhibitors. See Tables 3 and 4 for quality assessment of the studies and outcomes using the GRADE system.

Selective COX-2 Inhibitors in Cirrhotic Patients

In Claria et al a double-blind, randomized, placebo-controlled trial was conducted to investigate the effect of celecoxib, naproxen and placebo on renal function in patients with cirrhosis without previous hepatorenal syndrome. Twenty-eight patients with compensated cirrhosis and ascites were randomly assigned to receive short-term, twice-daily and anti-inflammatory dosing of celecoxib (COX-2 selective inhibitor), naproxen (non-selective COX
inhibitor), or placebo for a total of 5 doses, each with simultaneous oral use of furosemide. Randomization to treatment was determined by a random number generator. All investigators and subjects were blinded to sequence allocation, and all medications including placebo were manufactured by an independent pharmaceutical company to appear similarly. Subjects eligible for the study had met the criteria of diagnosis of cirrhosis, serum creatinine less than 1.5mg/dL, and without hepatic encephalopathy, bacterial infections, cardiorespiratory diseases, renal diseases, type 1 diabetes mellitus, peripheral vascular disease, hepatocellular carcinoma, treatment with beta-blockers, and history of peptic ulcer or gastrointestinal bleeding. Seven subjects were excluded from analysis after GFR measured below 40 mL/min. Data was analyzed using one-way analysis of variance and unpaired Student t tests. Baseline markers and parameters of liver, platelet aggregation, and renal functions were measured after a four-day wash-out period of all NSAIDs and diuretics. The results demonstrated no statistically significant derangements in GFR, urinary prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), renal plasma flow (RPF), inhibition of platelet aggregation (PA), and interference with efficacy of furosemide diuresis (V\textsubscript{furosemide}) were observed in the group treated with celecoxib or placebo, whereas the naproxen group showed statistically significant differences which are discussed in the next section. (See Table 2 for more detailed data.) The study concluded that celecoxib was renal-sparing, with effects similar to that of placebo, and safer than naproxen in patients with cirrhosis and ascites.

In a second study, effects of short-term use of celecoxib on renal function described by Guevara et al\textsuperscript{18} in a pilot quasi-experimental study, which included 9 patients with cirrhosis and ascites. No randomization or blinding was described. Patients with BUN > 40mg/dL, serum creatinine > 1.5 mg/dL, low platelet count, and gastrointestinal bleeding were excluded from the
study. All patients were placed on a controlled sodium diet of 50 mEq per day for 5 days prior, followed by a treatment with celecoxib 200 mg once daily for 5 consecutive days. In analyzing data, the non-parametric Wilcoxin test was utilized, which demonstrated no statistical significance in change in creatinine (0.7 ± 0.06 versus 0.8 ± 0.04 mg/dL) from baseline. Moreover, results demonstrated no significant reductions prior to and after treatment in GFR (74 ± 8 to 67 ± 8 mL/min), PGE2 (1429 ± 265 to 1053 ± 224 pg/min), PG 6-keto-F1α (2021 ± 298 to 1400 ± 269 pg/mL), urine sodium (4 ± 4 to 8 ± 6 mEq/L), and urine volume (1115 ± 87 to 1083 ± 89 mL/day) with short-term use of celecoxib. However, a decline in GFR of at least 20% was observed in 4 out of 9 patients. The conclusions of the pilot study suggested no renal dysfunction with short-term administration of 200 mg daily dose of celecoxib in patients with cirrhosis and ascites.18

**Non-selective COX inhibitors in cirrhotic patients**

As mentioned earlier, effects of naproxen were compared to celecoxib and placebo in a randomized controlled trial conducted by Claria et al.8 Findings of the study include statistically significant reduction in GFR in the group treated with naproxen (500mg BID for 5 doses), p < 0.05. Also, urinary PGE2, a marker for homeostatic control of renal vasodilatation and perfusion, was significantly reduced in the naproxen treatment group and spared in the celecoxib and placebo groups. Reduced renal plasma flow, inhibition of platelet aggregation, and dampened response to the diuretic furosemide measured in terms of urine volume were also demonstrated after 5 doses of naproxen and not in the other two groups. (See Table 2.) The study concluded that naproxen greatly affected renal function on a short-term course and should be avoided or used with great caution in patients with cirrhosis.8
Similar renal impairments were demonstrated in a randomized trial conducted by Brater et al in 1987, concerning the acute and chronic use of sulindac, ibuprofen and naproxen in 5 patients with cirrhosis. Subjects who had documented cirrhosis with ascites and no more than trace edema were recruited. All 5 patients were placed on a controlled sodium diet for 3 days, after which baseline blood and urine samples were obtained. All 5 patients received a single dose of sulindac 200mg. Also depending on tolerability, 4 out of 5 patients proceeded to receive a regimen of twice daily dosing of sulindac for 4 more days. One patient withdrew due to intolerance and health problems. Then an unspecified randomization scheme was utilized to assign patients to receive either ibuprofen or naproxen following a 5-day recovery period with sulindac use. Four patients continued to receive a single dose of either ibuprofen 600mg or naproxen 500mg. Two of four subjects tolerated without drastic decrements in creatinine clearance and continued on with thrice daily dosing of ibuprofen or twice daily dosing of naproxen for 4 more days. Four out of five patients experienced reduction in creatinine clearance after a single dose of sulindac. Two of four patients had significantly decreased creatinine clearance (116 ± 6.7 to 90 ± 3.0 mL/min, p-value < 0.05; 111 ± 5.9 to 89 ± 2.2 mL/min, p-value <0.05) with 4 additional days of exposure to sulindac. Two of two patients receiving additional doses of ibuprofen also experienced significant reduction in creatinine clearance (93 ± 3.6 to 78 ± 0.9 mL/min, p-value < 0.05; 111 ± 5.9 to 87 ± 4.6 mL/min, p-value <0.05). Interestingly, all patients except the withdrawn participant recovered from impairments in creatinine clearance after a 5-day recovery period post-treatment. This suggests derangements in renal function associated with non-selective COX inhibitors can be acute and largely reversible.

A quasi-experimental study conducted by Daskalopoulos et al investigated effects of indomethacin and sulindac on renal function and response to furosemide in 15 patients with
cirrhosis. Patients were confirmed to have cirrhosis on liver scan, biopsy or other standard
criteria. Nine patients received sulindac 150mg orally, while 3 of the patients in sulindac group
and 6 more received indomethacin 50mg orally, summing to 9 in the indomethacin group. On
day three, all patients received furosemide IV for evaluation of response to diuretics. A 5-day
washout period and controlled sodium diet were implemented before receiving treatment. No
randomization or control group was in place. The indomethacin treatment group demonstrated
significant reduction from basal measurements in urinary volume (90 ± 21 to 16 ± 5 mL/h, p-
value < 0.05), creatinine clearance (99 ± 18 to 45 ± 10 mL/min, p-value < 0.05), and urinary
PGE2 (27.9 ± 6.6 to 3.7 ± 1.1 ng/h, p-value < 0.01), whereas the sulindac treatment group did
not show statistically significant reductions in the corresponding parameters. Both the sulindac
and indomethacin groups showed significantly diminished response to furosemide diuresis in
urinary volume and urine sodium. Urinary volume in the group treated with both furosemide and
sulindac decreased from 365 ± 114 to 227 ± 151 mL/h, p-value < 0.05, and urinary sodium
dropped from 124 ± 60 to 60 ± 36 mEq/h, p-value < 0.05. Results of from the group treated with
indomethacin and furosemide showed a mean reduction in urinary volume, from 290 ± 50 to 130
± 54 mL/h, p-value < 0.01, and urinary sodium from 84 ± 28 to 28 ± 24 mEq/h, p-value < 0.05.
Moreover, PGE2 levels decreased significantly after administration of sulindac and furosemide
(p-value < 0.05) and indomethacin and furosemide (p-value < 0.02). Both medications impaired
renal function and response to furosemide. Effects are more pronounced with indomethacin than
sulindac on suppression of renal functions. 9

Another quasi-experimental study by Quintero et al19 measured the effects of short-term
use of sulindac on renal function in patients with cirrhosis and ascites arrived at similar
conclusions. Quintero et al measured GFR, free water clearance, PGE2 and PG 6-keto-EF_1α in 5
non-azotemic patients with cirrhosis and ascites before and after 3 days of sulindac 200mg twice daily dosing. No randomization or blinding was in place. Patients were placed a controlled sodium diet consisting of 50 mEq of sodium daily, and a 6-day wash-out period of NSAIDs, diuretics, and other medications. In addition, 6 healthy volunteers served as control for comparing serum levels of sulindac sulfide and sulindac sulfone, metabolites of sulindac. Results showed significant, across-the-board reductions after sulindac treatment in mean GFR (111 ± 15 to 67 ± 10 mL/min; p-value < 0.01), free water clearance (7.0 ± 1.5 to 3.7 ± 1.3; p-value < 0.02), urine volume (10.8 ± 1.8 to 6.3 ± 1.6 mL/min; p-value < 0.02), urine PGE2 (24.2 ± 5.5 to 3.8 ± 1.1 ng/h; p-value < 0.05), and PG 6-keto-EF₁α (19.9 ± 2.9 to 5.6 ± 1.1 ng/h; p-value < 0.02).

Additionally, serum levels of sulindac and sulindac sulfide were found to be four times higher than in healthy subjects, (p-value < 0.01). Quintero et al concluded that sulindac at 200mg twice daily, the recommended dosing for anti-inflammatory needs, produced marked impairments in GFR and production of renal prostaglandin in patients with cirrhosis and ascites, and thus monitoring is needed when administering sulindac and/or other NSAIDs.¹⁹

An earlier study by Brater et al⁶ conducted in 1986, 5 patients with cirrhosis in a quasi-experimental study were placed on a controlled sodium diet and diuretic washout-period for 5 days. Patients were confirmed to have no history of or concurrent renal insufficiency, and received a single 200mg dose of sulindac. Renal parameters were monitored for 4 or 5 additional days following treatment with sulindac for safety. Four patients experienced a transient decrease in creatinine clearance immediately after dose of sulindac, measured using inulin clearance. Mean creatinine clearance was 58.2 mL/min; however, statistical significance, standard error, and confidence intervals were not calculated. The reduction in creatinine clearance averaged 47.5% among the 4 patients. Creatinine clearance recovered to pre-treatment levels after a second
assessment 6 to 8 hours post-administration of sulindac. Brater et al concluded that sulindac produced the similar renal impairments as previously reported with other NSAIDs and should be used with caution.\textsuperscript{6}

**DISCUSSION**

**Renal Dysfunction in Non-Selective COX and Selective COX-2 Inhibitors**

Findings from the studies suggest that non-selective COX inhibitors markedly reduce renal function for the duration of use, however impairments are less pronounced in selective COX-2 inhibitors. Specifically, the reductions in creatinine clearance and/or GFR and prostaglandin levels were significantly more than levels corresponding to the use of selective COX-2 inhibitors. Although the level of evidence in the safety of selective COX-2 inhibitors in cirrhosis is immensely limited (see Tables 3 and 4), based on studies presented, selective COX-2 inhibitors likely affect renal function to a lesser extent than non-selective COX inhibitors. There does not appear to be a dose-dependent impairment from selected data. This finding suggests a potential role for selective COX-2 inhibitors administered for a limited course to address anti-inflammatory and analgesic needs in patients with cirrhosis.

**Reversibility of Renal Impairment, Suppression of Furosemide and Platelet Aggregation**

Secondary findings indicate that the suppressant effects on renal hemodynamics appear to be reversible upon termination of use of non-selective COX inhibitors, signified by recovery of creatinine clearance or GFR to near pre-treatment values.\textsuperscript{6,7} Although recovery from short-term imbalances in prostaglandins is possible, chronic use of NSAIDs might cause more severe renal impairments, such as hepatorenal syndrome, and more permanent injuries to the kidneys. In
addition, the co-administration of non-selective COX-inhibitors and furosemide appears to dampen the efficacy of furosemide, a vital diuretic in patients with compensated and decompensated cirrhosis and ascites. However, this effect on diuresis was not associated with selective COX-2 inhibitors. Furthermore, non-selective COX inhibitors decreased platelet aggregation in two studies, and corresponding changes were not large enough to be significant in selective COX-2 inhibitors. Inhibited platelet aggregation increases chances of bleeding, and more specifically esophageal variceal hemorrhage pertaining to patients with cirrhosis, portal hypertension, and existing esophageal varices. As bleeding from esophageal varices is difficult to treat and often results in fatality, non-selective COX inhibitors comparatively are associated with more risk of severe complications, despite the short course of treatment.

Limitations

Research on renal effects of NSAIDs in patients with pre-existing liver dysfunction is limited and was met with many challenges in identifying well-conducted studies. In fact, none of the available studies in the present had a design quality rated above “low” according to the GRADE system. The limited number of studies, small sample sizes of the studies available, and lack of randomization and blinding in the majority of trials limits the conclusions to be drawn and the strength of recommendations for clinical practice. The shortage of studies is reasonably expected due to the nature of the investigation revolving around a question of harm, which renders this topic less desirable to be repeated or conducted on a larger scale. This paper is meant to conduct a literature review to collect qualitative data from available studies and rate the level of evidence using the GRADE system, rather than pooling quantitative data from all studies after statistical adjustments, such as in a meta-analysis. Without further statistical manipulations, it is
difficult to draw quantitative conclusions due to the use of different COX inhibitors, different dosages and intervals of dosing, and different parameters to indicate renal function (GFR, creatinine clearance, and adjusted creatinine clearance using the Cockcroft-Gault formula).\textsuperscript{20} Therefore, inter-study statistical comparisons were not produced for the reasons narrated.

**CONCLUSION**

The safety of short-term administration of selective COX-2 inhibitors in cirrhosis is likely better than non-selective COX inhibitor, which constitutes a weak recommendation due to poor quality of evidence. Furthermore, great caution needs to be exercised in monitoring renal function when placing cirrhotic patients on non-selective COX inhibitors. Therefore, more well-conducted studies are necessary to provide adjunctive evidence to support this finding. For future research, the role of prostaglandin supplementation while taking NSAIDs may be investigated, as an effort to identify possible venues to allow safer use of NSAIDs in the future for anti-inflammatory needs in patients with cirrhosis.
REFERENCES


Table 1. List of selective COX-2 inhibitors and non-selective COX inhibitors

<table>
<thead>
<tr>
<th>Selective COX-2 inhibitors</th>
<th>Non-selective COX inhibitors</th>
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<tr>
<td>Celecoxib</td>
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<tr>
<td>Valdecoxib</td>
<td>Diflunisal</td>
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<td>Rofecoxib</td>
<td>Etodolac</td>
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<td></td>
<td>Fenoprofen</td>
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<td>Flurbiprofen</td>
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<td>Ibuprofen</td>
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<td>Indomethacin</td>
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<td>Ketoprofen</td>
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<td>Ketorolac</td>
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<td>Mefenamic acid</td>
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<td>Nabumetone</td>
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<td>Piroxicam</td>
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<td>Sulindac</td>
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<td>Tolmetin</td>
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Table 2. GFR, PGE2, RPF, inhibition of PA, and suppression of furosemide diuresis before and after treatment with celecoxib (n = 7), naproxen (n = 6), and placebo (n = 5) in Claria et al.

<table>
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<tr>
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<th>Celecoxib</th>
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<th>Placebo</th>
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<td>Before</td>
<td>After</td>
<td>P</td>
<td>Before</td>
<td>After</td>
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<td>GFR (mL/min)</td>
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<td>105 ± 14</td>
<td>NS</td>
<td>113 ± 27</td>
<td>84 ± 22</td>
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<td>85 ± 11</td>
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<td>PGE2 (pg/min)</td>
<td>3609 ± 678</td>
<td>3278 ± 1.052</td>
<td>NS</td>
<td>11.6 ± 3.4</td>
<td>9.4 ± 2.9</td>
<td>&lt;0.01</td>
<td>6523 ± 1194</td>
<td>10339 ± 5648</td>
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<td>RPF (mL/min)</td>
<td>536 ± 60</td>
<td>483 ± 65</td>
<td>NS</td>
<td>592 ± 158</td>
<td>429 ± 106</td>
<td>&lt;0.04</td>
<td>417 ± 62</td>
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<td>PA (%)</td>
<td>68 ± 12</td>
<td>71 ± 18</td>
<td>NS</td>
<td>72 ± 8</td>
<td>47 ± 8</td>
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<td>V_furosemide (mL/h)</td>
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<td>--</td>
<td>NS</td>
<td>561 ± 128</td>
<td>414 ± 107</td>
<td>&lt;0.05</td>
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Table 3. Characteristics of reviewed studies, GRADE profile of studies involving use of selective COX-2 inhibitor in cirrhosis

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Characteristics of reviewed studies</th>
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<tr>
<td>Downgrade Criteria</td>
<td>Quality assessment</td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design Limitations Indirectness Imprecision Inconsistency Publication bias likely Study Treatment (total) Placebo or no treatment (total)</td>
</tr>
<tr>
<td>Reduction in GFR</td>
<td>2 1 RCT 1 QES Very serious limitations a No serious indirectness Serious imprecision No serious inconsistencies No bias likely Claria et al 9/28 9/28 Very low Critical</td>
</tr>
<tr>
<td>Reduction in urinary prostaglandin level</td>
<td>2 1 RCT 1 QES Very serious limitations a No serious indirectness Serious imprecision No serious inconsistencies No bias likely Claria et al 9/28 9/28 Very low Critical</td>
</tr>
<tr>
<td>Inhibition of platelet aggregation</td>
<td>1 1 RCT Serious limitations b No serious indirectness No serious imprecision No serious inconsistencies No bias likely Claria et al 9/28 9/28 Low Important</td>
</tr>
<tr>
<td>Dampening effect on concurrent furosemide diuresis</td>
<td>1 1 RCT Serious limitations b No serious indirectness No serious imprecision No serious inconsistencies No bias likely Claria et al 9/28 9/28 Low Important</td>
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</tbody>
</table>

a Limitations in sample sizes and study designs: Claria et al: n = 9 for celecoxib group, total n = 28, and 7 subjects withdrawn from study; Guevara: n = 9 without control group, no randomization, blinding, or report of statistical significance

b Wide 95% confidence intervals in Guevara et al with respect to GFR and urinary prostaglandin levels

RCT = randomized controlled trial
QES = quasi-experimental study
Table 4. Characteristics of reviewed studies, GRADE profile of studies involving use of non-selective COX inhibitors in cirrhosis

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Characteristics of reviewed studies</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Downgrade Criteria</td>
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<tr>
<td>No. of Studies</td>
<td>Design</td>
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<tr>
<td>5</td>
<td>2 RCT</td>
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<tr>
<td>5</td>
<td>2 RCT</td>
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<tr>
<td>2</td>
<td>1 RCT</td>
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</tbody>
</table>

Reduction in creatinine clearance

- Claria et al
- Brater et al 1987
- Daskalopoulos et al
- Quintero et al

Reduction in urinary prostaglandin level

- Claria et al
- Brater et al 1987
- Daskalopoulos et al
- Quintero et al

Inhibition of platelet aggregation

- Claria et al
- Brater et al 1987

Dampening effect on concurrent furosemide diuresis

- Claria et al

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* Limitations in sample sizes and study designs: Claria et al: n = 10 for Naproxen group, total n = 28; Brater 1987: n = 5, no randomization, blinding, or control, no reported statistical significance or confidence intervals; Daskalopoulos: n = 15, no randomization, blinding, or control; Brater 1986: n = 5, randomized without blinding or control group, 1 subject withdrew early from study; Quintero et al: n = 5, no randomization, blinding, or control

* Wide standard errors and 95% confidence intervals in Claria, Daskalopoulos, and Quintero et al

* Significant reductions in creatinine clearance was seen with sulindac treatment in Brater 1987 and Quintero et al while no significance was found in Daskalopoulos et al.