Original Article
Celebrex combined with omeprazole to reduce gastrointestinal adverse reactions caused by Celebrex alone in treating Chinese elderly patients with osteoarthritis

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Abstract: Objective: To investigate the effects of Celebrex combined with omeprazole in treating elderly osteoarthritis (OA) patients with a high risk of gastrointestinal (GI) adverse reactions, indicated by a history of gastroduodenal ulcer or concurrent usage of aspirin, anticoagulants and corticosteroids. Methods: From April 2013 to April 2014, 400 patients (60-75 years old) were divided into 2 groups at a ratio of 1:1. The intervention group was treated with Celebrex (200 mg, bid) combined with omeprazole (20 mg, qd), and the control group was given Celebrex (200 mg, bid) and placebo (1 tablet, qd). The patients were treated continuously for 3 months and evaluated by follow-up every 2 weeks. Arthritic pain was measured using the visual analogue scale (VAS); GI symptoms and platelet adverse reactions were also recorded. Results: 35 patients (17.9%) in the control group dropped out the therapy due to adverse events; 18 patients (9.2%) dropped out of the intervention group with the difference being statistically significant (P = 0.040), which means that the combination regime increased the patients’ tolerance to GI adverse reactions. In the control group, common GI adverse events were: 22, dyspepsia (11.2%); 21, abdominal pain (10.7%); 16, diarrhea (8.2%). The incidence of adverse events was obviously reduced in the intervention group, which included: 9, dyspepsia (4.6%); 8, abdominal pain (4.1%); 13, diarrhea (6.7%). The incidence of dyspepsia, abdominal pain and nausea were significantly different (P<0.05). Conclusion: A combination of Celebrex and omeprazole significantly reduced the incidence of GI adverse reactions in Chinese OA patients.

Keywords: COX-2, diarrhea, dyspepsia, gastrointestinal, nausea, NSAIDs, osteoarthritis, PPI

Introduction

Chronic orthopedic pain caused by osteoarthritis, rheumatoid arthritis (RA) and osteoporosis is normally treated with non-steroidal anti-inflammatory drugs (NSAIDs), opioids and hormones. NSAIDs include selective and non-selective classes; non-selective NSAIDs simultaneously inhibit COX-1 (cyclooxygenase-1) and COX-2 (cyclooxygenase-2), while selective drugs inhibit COX-2 only. It is well known that COX-1 plays a role in gastrointestinal protection and that COX-2 is mainly responsible for the pain induced by inflammation [1-4]. By selectively inhibiting COX-2, the gastrointestinal adverse events can be prevented when selective NSAIDs are used to treat inflammation and pain [5].

In the late 1990s, the first COX-2 selective NSAID, celecoxib (Celebrex) was developed, which is used to treat the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation, and juvenile rheumatoid arthritis in patients non-selective class [2, 6]. Later, selective NSAIDS such as vivox and bextra were developed but they were removed from the market by the US FDA due to unacceptable adverse effects on patient health. Celebrex remains the only available COX-2 inhibitor approved by the FDA but with additional warnings added to the prescribing instructions (US FDA website).

Celebrex increases the risk of severe cardiovascular and thromboembolic events, myocardial
COX-2 inhibitor plus PPI reduces GI adverse effects in OA patients

Infarction and stroke, as well as GI adverse reactions [7-9].

In patients treated long-term with selective COX-2 inhibitors, it has been proven that proton pump inhibitors (PPI) help to ameliorate effectively symptoms such as heartburn, reflux and upper abdominal pain [10, 11]. Omeprazole is a PPI, blocking the enzymes CYP2C19 and CYP3A4 [12], and is used for the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease and laryngopharyngeal reflux [13-16]. Furthermore, studies on arthritic patients at risk of GI symptoms have recommended the use of a non-selective NSAID with PPI or a COX-2 selective NSAID [17-19].

Many studies have compared the therapeutic effects of these two classes of drugs. Rahme and colleagues [20] retrospectively analyzed a total of 332,491 patients treated from 1999 to 2002, and found that the combinatory use of PPI and selective COX-2 inhibitors enhanced gastrointestinal protection in patients older than 75 years. However, prospective evidence is still needed, especially for elderly Chinese OA patients with gastrointestinal complications. The safety of selective COX-2 inhibitors is not clear in these patients, nor the potential protective effects of the combinatory use of these two drug classes. Therefore, we conducted a prospective randomized controlled study by recruiting elderly Chinese OA or RA patients (60-75 years old) with a history of diagnosed gastro-duodenal ulcer to our study and evaluated the effects of gastrointestinal protection using a combination of Celebrex and omeprazole.

Materials and methods

Patient characteristics

A total of 400 patients were recruited into the 12-week randomized control study based on our inclusion criteria. The hospital ethics committee approved the protocol and written informed consent was obtained from all participants. Celebrex was provided by Pfizer China Co. LTD, and omeprazole together with the placebo, was provided by the Jiangsu Changzhou Fourth Pharmaceutical Factory, China. All participants were divided into two groups: the control group was given Celebrex (200 mg, bid) and placebo (1 tablet, qd), while the intervention group was treated with Celebrex (200 mg, bid) combined with omeprazole (20 mg, qd). The patients were treated continuously for three months and evaluated by follow-up every 2 weeks. GI functions and tolerance to the treatment were evaluated based on GI symptoms.

Inclusion and exclusion criteria

Inclusion criteria were: 1) age: 60-75 years old; 2) history of OA or RA ≥6 months; 3) history of confirmed diagnosis of peptic ulcer; 4) under or not under treatment with aspirin, anticoagulants or corticosteroids.

Exclusion criteria were: 1) history of drug allergy; 2) PPI intolerance; 3) history of myocardial infarction, stroke, active peptic ulcer; 4) history of alcohol or drug abuse. There were 200 participants in each group at the beginning. In the control group, 4 of the patients were lost and 35 dropped out due to endpoint events. In total, 196 participants participated according to the protocol and 161 of them completed the study. In the intervention group, 5 patients were lost and 18 dropped out due to endpoint events. Thus, 195 patients participated according to the protocol and 177 of them finished the study (Figure 1).

Figure 1. Study flow diagram of 400 patients. Nine patients dropped out because of families' and patients' wills. 391 patients were analyzed and 196 patients were assigned to the monotherapy group and 195 to the combination group. 35 patients stopped the trial because of adverse events in monotherapy and 18 patients stopped in the combination group.
Primary endpoint

To measure the incidence of GI adverse events with an evaluation of GI tolerability; GI symptoms were recorded as the frequency of gastric hyperacidity, stomach ache, nausea or vomiting, gastric pain, heart burn after a meal, abdominal distention, early satiety, belching, gastric discomfort in the morning and a tarry stool.

Scheduled evaluations and records were kept for the GI symptoms described above after the treatment, and among them, common ailments included dyspepsia, abdominal pain, diarrhea, abdominal distension and constipation. Routine blood tests were performed and hemoglobin and hematocrit levels measured. Severe adverse reactions included GI bleeding, perforation and pyloric obstruction.

Secondary endpoint

Scenarios that prevented patients from continuing the study included severe adverse reactions, a decrease of hemoglobin to \( \leq 2\) g/dL, a ratio of the hematocrit decrease \( >10\%\), or a patient’s request to stop the study due to adverse effects.

Other endpoints

Evaluation of the efficacy of a COX-2 selective inhibitor given as a treatment for joint pain was dependent on a visual analogue scale (VAS) assessment. VAS joint pain was conducted before the start of the study and every month. A VAS assessment was conducted to confirm joint pain with the VAS scores ranging from 0 mm (no pain) to 100 mm (intolerable pain). Tolerable joint pain was defined as 25 mm of the VAS score in the present study.

Table 1. Baseline characteristics of patients in the two groups

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>C + O</th>
<th>P</th>
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<tbody>
<tr>
<td>Age</td>
<td>66.3 ± 5.4</td>
<td>67.2 ± 5.2</td>
<td>0.094</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>0.341</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37.8 (74)</td>
<td>32.8 (64)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62.2 (122)</td>
<td>67.2 (131)</td>
<td></td>
</tr>
<tr>
<td>Disease (%)</td>
<td>0.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>184 (93.9)</td>
<td>170 (87.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>12 (6.1)</td>
<td>25 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Medication (%)</td>
<td>0.811</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>26 (13.3)</td>
<td>33 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>8 (4.1)</td>
<td>7 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>8 (4.1)</td>
<td>9 (4.6)</td>
<td></td>
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</table>

Table 2. The incidence of GI adverse events after treatment (N%)

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>C + O</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>22 (11.2)</td>
<td>9 (4.6)</td>
<td>0.039</td>
</tr>
<tr>
<td>Stomachache</td>
<td>21 (10.7)</td>
<td>8 (4.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (7.7)</td>
<td>5 (2.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (8.2)</td>
<td>13 (6.7)</td>
<td>0.701</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (3.6)</td>
<td>6 (3.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>7 (3.6)</td>
<td>6 (3.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total</td>
<td>88 (44.9)</td>
<td>47 (24.1)</td>
<td></td>
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</table>

Statistical analysis

Statistical analysis of the experimental data was performed using SPSS, version 18.0, software (IBM). Normally distributed data are presented as the mean ± standard deviation (x ± s). A chi-square test was used to compare the 2 groups and a chi-square trend analysis to determine trends between multiple groups. \( P<0.05\) was considered to be statistically significant.

Results

Baseline characteristics of patients in the 2 groups

A total of 400 patients (age range 60-75 years) were divided into 2 groups: the control group C and intervention group (C + O) for the 3-month study. The baseline information was similar in the 2 groups. Female patients accounted for a larger proportion in both groups. The ratio of patients presented as OA was 93.9% or 87.2% for each group. No significant differences were observed following the use of aspirin, anticoagulants and glucocorticoids (Table 1), so these 2 groups were comparable.

Incidence of GI adverse events

In the control group, the incidence of adverse events were recorded as 11.2% for dyspepsia, 10.7% for abdominal pain, 8.2% for diarrhea, 7.7% for nausea, 3.6% for constipation and 3.6% for abdominal distention. In the intervention group, the incidence of adverse events were 4.6% for dyspepsia, 4.1% for abdominal pain, 6.7% for diarrhea, 2.6% for nausea, 3.1% for constipation and 3.1% for abdominal disten-
COX-2 inhibitor plus PPI reduces GI adverse effects in OA patients

The combination of Celebrex and omeprazole significantly reduced the incidence of dyspepsia, abdominal pain and nausea (Table 2).

Changes of hemoglobin and hematocrit

When patients in the control group were treated with Celebrex alone (161 cases), the decrease of hemoglobin was 0.25 ± 0.43 g/dL during the 12-week study. The hemoglobin decrease was 0.23 ± 0.42 g/dL in the intervention group but both were smaller than 2 g/dL. The decrease in the hematocrit was 0.76 ± 0.39% in the control group and 0.71 ± 0.39% in the intervention group, both of which were smaller than 10%. The GI tolerability was generally satisfactory in both groups, but 35 patients in the control group and 18 patients in the intervention group dropped out of the study because their hemoglobin decrease was greater than 2 g/dL or the hematocrit decrease exceeded 10% of the baseline value.

Incidence of drop-out

In the control group, a total of 161 patients finished the treatment, 4 patients were lost to follow-up and 35 dropped out. In the intervention group, 177 patients finished the treatment, 5 patients were lost in the follow-up and 18 patients dropped out. Overall, the incidence of dropout for GI adverse events was 17.9% in the control group and 9.2% in the intervention group, and the difference was significant between the 2 groups as shown in Table 3.

Therapeutic effects

Before the corresponding treatment, 85.2% and 87.2% of the patients presented with arthritic pain in the 2 groups, a difference that was not significant. There was no statistically significant difference between the monotherapy group and the combination therapy group (P>0.05). The number of patients who scored <25 mm on VAS increased significantly from baseline in both groups (P<0.000, Table 4).

In the present study, the incidence of dropout was significantly lower in the intervention group (Celebrex combined with omeprazole) than the control group who were given only Celebrex (P<0.05).

In terms of all the common adverse reactions, the intervention group had a lower incidence of GI adverse reactions compared with the group receiving only Celebrex. These findings were statistically significant for most adverse events (P<0.05), including dyspepsia, abdominal pain and nausea. The results suggested that instead of using selective the COX-2 inhibitor Celebrex alone, a combinatory regime with a PPI guaranteed better GI tolerability and adherence to the treatment; this approach should be further promoted in clinical practice.

However, the incidence of adverse reactions in the control group were 11.2% for dyspepsia, 10.7% for abdominal pain, 8.2% for diarrhea, 7.7% for nausea, 3.6% for constipation and 3.6% for abdominal distention. The adverse reactions were significantly higher than the results published by Mallen et al., which were 5.5% for dyspepsia, 5.1% for abdominal pain, 4.8% for diarrhea, 3.0% for nausea, 1.2% for constipation and 1.6% for abdominal distention, respectively. The findings may be explained as follows: First, the patients included in our study were older, and may have presented with a history of peptic ulcer or concurrent use of aspirin, anticoagulants and/or corticosteroids. Thus, it was not surprising that higher incidences of GI adverse events were observed in our study. Second, it was noted that the potential differences in the incidence of constipation, diarrhea and abdominal distention were not significant and likely attributable to the limitations of mucosal protective drugs.

At present, when NSAIDs are prescribed, the commonly used GI mucosal protectants include PPI, prostaglandins and H2-receptor antagonists, with PPI being the most popular initial therapy [21]. PPIs prevent NSAID-induced GI peptic ulcers and promote healing of gastroduodenal ulcers in arthritic patients [22, 23]. The administration of a COX-2-selective inhibitor plus PPI completely prevented GI bleeding [24], mucosal apoptosis and lesion production in mice [25].

Table 3. Reasons for dropout

<table>
<thead>
<tr>
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<th>C (n = 196)</th>
<th>C + O (n = 195)</th>
<th>P</th>
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<tbody>
<tr>
<td>GI adverse events/endpoints</td>
<td>35 (17.9%)</td>
<td>18 (9.2%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4 (2.0%)</td>
<td>5 (2.6%)</td>
<td>P&gt;0.05</td>
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</table>
Even though PPI therapy is thought to be convenient, effective and reliable, its mechanism of reducing gastric acid production limits its protective effects to the upper digestive tract. Considering that the damage to the intestine or colon is not dependent on acid [9, 26, 27], PPI provides relatively limited protection to the lower digestive tract. Symptoms such as constipation, diarrhea and abdominal distension are mainly associated with damage to the lower digestive tract. In fact, NSAID rarely cause discomfort or disease of the small intestine and colon. Thus, it is a worthwhile endeavor to develop an effective regime to protect patients using NSAIDs from the adverse effects caused by damage to the lower digestive tract.

In the present study, we noticed an obvious reduction of the patient arthritic pain and GI adverse effects after 3 months of treatment in the combination group, which supported the results in Japanese patients published by Hasegawa and colleagues [28]. Although the reduction in the VAS scores was not significant between the 2 groups, we noticed a significant improvement in arthritic pain management after 3 months in both groups. However, there were some limitations to our study. We used a combination of hemoglobin and hematocrit as a surrogate for measuring blood loss, which potentially could be delayed and inaccurate. Moreover, follow-ups combined with GI endoscope examinations would make evaluation of GI injury caused by NSAIDs more objective and unequivocal.

**Conclusion**

In patients >60 years of age, with a high risk of GI complications, a combination of selective COX-2 inhibitors and PPI is recommended when prescribing NSAIDs. Compared with using selective COX-2 inhibitors alone, this regime will reduce the potential damage caused by NSAIDs and improve the tolerance to NSAIDs. Either Celebrex alone or the addition of a PPI will effectively benefit OA patients by ameliorating arthritic pain.

**Disclosure of conflict of interest**

None.

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**References**


COX-2 inhibitor plus PPI reduces GI adverse effects in OA patients


[26] Bjarnason I and Takeuchi K. Intestinal permeability in the pathogenesis of NSAID-induced
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