Original Article

Anti-reflux effects of pantoprazole combined with mosapride and domperidone in the treatment of obstructive sleep apnea hypopnea syndrome and laryngopharyngeal reflux disease

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Abstract: Objective: To explore the anti-reflux effects of pantoprazole combined with mosapride and domperidone in the treatment of obstructive sleep apnea hypopnea syndrome (OSAHS) and laryngopharyngeal reflux disease (LPRD). Methods: A total of 92 patients with OSAHS and LPRD were divided into the control group (n=45, treated with pantoprazole combined with mosapride and domperidone) and the observation group (n=47, pantoprazole monotherapy) according to random number tables. All patients took the medications for 8 weeks. Pulmonary function parameters and sleep quality indexes before and after treatment were compared. The results of reflux symptom index (RSI), reflux finding score (RFS) and arterial blood gas (ABG) analysis before treatment and after 8 weeks of treatment were also compared. Results: The observation group had significantly higher total rate of effective treatment than the control group (95.74% vs. 71.11%, P=0.001). The observation group also had significantly higher vital capacity (VC), ratio of forced vital capacity compared to predicted values (FVC%), ratio of diffusing capacity divided by the alveolar volume compared to predicted values (DLCO/VA%), ratio of forced expiratory volume in one second compared to predicted values (FEV1%), total lung capacity (TLC) than the control group 8 weeks after treatment (all P<0.01). The observation group had significantly lower proportion of stage I sleep, apnea hypopnea index (AHI), and arousal index (AI) than the control group (all P<0.001). The proportion of stage III sleep for the observation group was significantly higher than that for the control group (P<0.001), and there was no statistically significant difference in the proportion of stage II sleep between the two groups (P>0.05). The proportion of patients whose RSI was above 13 and RFS above 7 in both groups decreased significantly after 8 weeks of treatment (both P<0.05), and the drop was more noticeable in the observation group (P<0.001). Both groups showed improvements in the results of ABG analysis after treatment (both P<0.05), but there was no statistically significant difference between the two groups (P>0.05). Conclusions: Pantoprazole combined with mosapride and domperidone can significantly improve lung function, sleep quality and acid reflux symptoms for patients with OSAHS and LPRD.

Keywords: Pantoprazole, mosapride, domperidone, obstructive sleep apnea hypopnea syndrome, laryngopharyngeal reflux disease

Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS), a special respiratory disease, is characterized by snoring, daytime sleepiness and apneas during sleep due to upper airway collapse and central respiratory regulation disturbance [1]. It is particularly common among the middle-aged and the obese, and is directly caused by narrowing and obstruction of the upper airway while sleeping [2]. OSAHS can severely affect the sleep quality of patients, and cause repetitive episodes of apneas during sleep. Patients with OSAHS are more likely to develop hypercapnia because of reductions in oxygen levels and increased carbon dioxide concentration in the blood. They are also at greater risk of high blood pressure, coronary heart disease, diabetes, cerebrovascular diseases, and even sudden unexpected death at
In addition, severe daytime drowsiness and fatigue make them more prone to all kinds of accidents (e.g. traffic accidents).

OSAHS patients often suffer many other systemic diseases, including laryngopharyngeal reflux disease (LPRD), which is a common reflux laryngitis, and has caught the attention of otolaryngologists in recent years [4]. According to the statistics, LPRD is present in up to 50% of patients with hoarseness and accounts for about 10% of patients who visit the department of otolaryngology [5]. LRPD is defined as the reflux of gastric contents into the larynx and pharynx, which can irritate the pharyngeal and laryngeal mucosa, damage the lining of the esophagus, and trigger vasovagal reflex, resulting in symptoms of sensation of a lump in the throat, hoarseness, difficulty in speaking and cough. At present, the mechanism behind the correlation OSAHS and LPRD is still unclear. However, the coexistence of LPRD in many OSAHS patients has concerned many scholars.

Medications including pantoprazole are commonly used to treat OSAHS and LPRD [6]. Pantoprazole, as a common antiulcer drug, can inhibit the secretion of gastric acids, and decrease the frequency of gastric acid reflux, so as to reduce patients’ awakening from sleep because of foreign body sensation in the throat [7]. But its effects in controlling the acid reflux and improving sleep are far from satisfactory. Mosapride is mainly used to treat functional dyspepsia and reflux diseases. It can enhance gastrointestinal mobility, accelerate gastric emptying, and prevent acid reflux [8]. Domperidone is a prokinetic agent, and can significantly relieve vomiting of various reasons and reduce the frequency of backflow of gastric contents [9]. All these three medications can treat OSAHS and LPRD, but there are few reports on the efficacy of their combined use.

Therefore, we used pantoprazole, mosapride and domperidone in combination for the treatment of OSAHS and LPRD, and explored the effects of this drug combination in improving patients’ sleep quality and controlling acid reflux, so as to provide a reference for the treatment of such diseases.

### Materials and methods

#### Patients

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Wenzhou Medical University. A total of 92 patients with OSAHS and LPRD admitted to The Second Affiliated Hospital of Wenzhou Medical University from December 2017 to January 2019 were selected as subjects and divided into the control group (n=45) and the observation group (n=47) according to random number tables. There was no statistically significant difference in baseline information between the two groups (P>0.05). See Table 1.

Inclusion criteria: Patients met diagnostic criteria for OSAHS established by The European Respiratory Society and the American Thoracic Association in 2002, and had LRPD as confirmed by the gastroscopy [10]; all patients were treated and received the tested medications for the first time; patients had no serious cardiovascular and cerebrovascular diseases, or kidney and liver diseases; patients participated in this study and signed the informed consent of their own free will.

Exclusion criteria: Patients were allergic to the tested drugs; patients had lung cancer, respiratory failure or serious liver diseases; patients had immune system diseases, blood diseases or endocrine diseases; patients had malignant tumors; patients were pregnant or lactating.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (n=45)</th>
<th>Observation group (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>29/16</td>
<td>29/18</td>
</tr>
<tr>
<td>Average age (year)</td>
<td>47.3±14.0</td>
<td>47.3±14.5</td>
</tr>
<tr>
<td>Average course of disease (year)</td>
<td>4.96±1.14</td>
<td>5.01±1.37</td>
</tr>
<tr>
<td>Clinical symptoms/cases (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensation of a lump in the throat</td>
<td>43 (95.56)</td>
<td>45 (95.74)</td>
</tr>
<tr>
<td>Trouble speaking</td>
<td>42 (93.33)</td>
<td>44 (93.62)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>44 (97.78)</td>
<td>46 (97.87)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>42 (93.33)</td>
<td>44 (93.62)</td>
</tr>
<tr>
<td>Dry and sore throat</td>
<td>44 (97.78)</td>
<td>45 (95.74)</td>
</tr>
</tbody>
</table>

The table above shows the comparison of baseline information between the two groups (P>0.05).
Medications

All patients were treated with Pantoprazole Sodium enteric-coated capsules (Hangzhou East China Pharmaceutical Group Co., Ltd.). One capsule (40 mg) was taken by mouth before breakfast per day for 8 weeks. Patients in the observation group were also given Mosapride Citrate tablets (Sumitomo Dainippon Pharma Co., Ltd.), and Domperidone tablets (Zhejiang Anglikang Pharmaceutical Co., Ltd.). One Mosapride tablet (5 mg) was taken by mouth before meals 3 times a day for 8 weeks, and one Domperidone tablet (10 mg) was taken by mouth half an hour before meals 3 times a day for 8 weeks.

Observation indexes and assessment criteria

Efficacy of treatment: Efficacy of treatments was evaluated according to patients’ sleep quality and the recovery of their laryngopharyngeal mucosa [11]. It was divided into 3 categories. Marked effect: clinical symptoms disappeared with significantly improved sleep quality and a near complete recovery of the laryngopharyngeal mucosa as confirmed by the laryngoscopy; effective: clinical symptoms and sleep quality showed improvement, with a partial recovery of the laryngopharyngeal mucosa as confirmed by the laryngoscopy; ineffective: symptoms remained basically unchanged, or even worsened. Total rate of effective treatment = number of patients who had effective treatment or for whom treatment effect was marked/total number of patients × 100%.

Pulmonary function parameters: Pulmonary function parameters including vital capacity (VC), total lung capacity (TLC), ratio of forced vital capacity compared to predicted values (FVC%), ratio of diffusing capacity divided by the alveolar volume compared to predicted values (DLCO/VA%), and ratio of forced expiratory volume in one second compared to predicted values (FEV1%) were measured. The JAEGER® Oxycon pro Spirometer (Shanghai CareFusion Trading Co., Ltd.) was used to test patients’ pulmonary function before admission and on the last day of treatment.

Sleep quality: Polysomnography (PSG) was performed before treatment and the next day after all treatment was given. Data including constituent ratio of sleep, apnea hypopnea index (AHI), and arousal index (AI) were compared. The constituent ratio of sleep refers to the proportions of different sleep stages during a whole sleep time. The AHI refers to the number of apneas and hypopneas a person experiences per hour of sleep. The arousal index refers to the number of arousals a person experiences per hour of sleep. AHI above 5 was indicative of OSASH.

The reflux symptom index (RSI), the reflux finding score (RFS), and arterial blood gas (ABG) analysis: The RSI and RFS scores, arterial partial pressure of oxygen (PaO₂) and arterial partial pressure of carbon dioxide (PaCO₂) of the two groups were compared before treatment and on the next day after all treatment was given. The arterial blood was drawn from the patients when they were in a resting state and were not breathing in oxygen. The PaO₂ and PaCO₂ were measured by the PL2000PLUS blood gas analyzer (Beijing Perlong New Technology Co., Ltd.). The RSI and RFS were used to rate the severity of LPRD before and after treatment. The RSI is a nine-item self-administered outcome questionnaire designed to document LPR symptoms and severity. Patients were asked to rate how nine problems have affected them over the past month on a scale of 0 (no problem) to 5 (severe problem), with a maximum total score of 45. RFS is an eight-item index designed to assess clinical severity of LFR. Scores range from 0 (normal) to 26 (most severe) [12]. RSI greater than 13 or RFS higher than 7 was considered to indicate LPRD. The proportion of patients with positive diagnosis of LPR in the two groups was compared. Specific symptoms for both instruments were shown in Table 2.

Statistical methods

The SPSS 21.0 statistical software was used to analyze data. The measurement data were expressed as mean ± standard deviation (X ± sd). One sample t-test was used for comparison between the two groups. Paired t-test was used for comparison within groups before and after treatment, and was expressed as t. Rank variables were compared with Mann-Whitney U test, and were expressed as H. Enumeration data were expresses as n (%), and were compared with χ² test and Fisher’s exact probability test.

Results

Comparison of efficacy of treatment between the two groups

The observation group had significantly higher total rate of effective treatment than the con-
Pantoprazole, mosapride and domperidone

Comparison of pulmonary function parameters between the two groups before and after treatment

There was no statistically significant difference in VC, TLC, FVC%, DLCO/VA%, and FEV1% between the two groups before treatment (all P>0.05). Both groups showed increases in VC, TLC, FVC%, DLCO/VA% and FEV1% after treatment, and the observation group had significantly higher VC, TLC, FVC%, DLCO/VA% and FEV1% than the control group (all P<0.01). See Table 4 and Figure 1.

Comparison of sleep quality indexes between the two groups before and after treatment

There was no statistically significant difference in the indexes of sleep quality between the two groups before treatment (all P>0.05). Both groups showed improvements in the indexes of sleep quality after treatment (all P>0.05). The observation group had significantly lower proportion of stage I sleep, apnea hypopnea index, and arousal index (all P<0.001), and higher pro-
portion of stage III sleep than the control group (P<0.001). And there was no statistically significant difference in the proportion of stage II sleep between the two groups (P>0.05). See Table 5 and Figure 2.

**Comparison of severity of LPRD and ABG results between the two groups before and after treatment**

There was no statistically significant difference in the severity of LPRD and results of ABG between the two groups before treatment (both P>0.05). The number of patients whose RSI was above 13 and RFS above 7 in both groups decreased after treatment (both P<0.05), and the decrease was more significant in the observation group (P<0.001). Both groups showed improvements in the results of ABG after treatments (both P<0.05), but there was no statistically significant difference between the two groups (P>0.05). See Table 6 and Figure 3.

**Discussion**

OSAHS is a potentially fatal sleep disorder, which is caused by narrowing and obstruction of the upper respiratory tract, resulting from

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**Table 5. Comparison of sleep quality indexes between the two groups before and after treatment (X ± sd)**

<table>
<thead>
<tr>
<th></th>
<th>Proportion of stage I sleep (%)</th>
<th>Proportion of stage II sleep (%)</th>
<th>Proportion of stage III sleep (%)</th>
<th>AHI (events per hour)</th>
<th>AI (events per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (n=45)</td>
<td>15.55±3.34</td>
<td>58.35±2.64</td>
<td>2.53±0.31</td>
<td>5.56±1.07</td>
<td>35.99±10.91</td>
</tr>
<tr>
<td>Observation group (n=47)</td>
<td>15.56±3.32</td>
<td>58.26±2.82</td>
<td>2.54±0.33</td>
<td>5.57±1.02</td>
<td>36.16±10.83</td>
</tr>
<tr>
<td>t</td>
<td>0.014</td>
<td>0.158</td>
<td>0.150</td>
<td>0.046</td>
<td>0.075</td>
</tr>
<tr>
<td>P</td>
<td>0.989</td>
<td>0.875</td>
<td>0.881</td>
<td>0.963</td>
<td>0.940</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (n=45)</td>
<td>13.43±1.45*</td>
<td>56.13±2.05*</td>
<td>3.69±0.21*</td>
<td>4.88±0.82*</td>
<td>28.88±7.91*</td>
</tr>
<tr>
<td>Observation group (n=47)</td>
<td>12.14±1.69*</td>
<td>56.04±2.09*</td>
<td>4.74±0.11*</td>
<td>3.32±0.83*</td>
<td>20.54±7.59*</td>
</tr>
<tr>
<td>t</td>
<td>3.922</td>
<td>0.208</td>
<td>29.849</td>
<td>9.065</td>
<td>5.161</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.835</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: *Compared with before treatment, P<0.05. AHI, apnea hypopnea index; AI, arousal index.
deviated nasal septum, enlarged tonsils, retrognathic mandible, long soft palate, and other abnormal tissues and structures [13]. At present, both surgical and non-surgical treatments are used to treat OSAHS, with the purpose of correcting tissue deformities. And nasal continuous positive airway pressure therapy is the preferred treatment, which requires no medications and has desirable efficacy.

LPRD is often caused by corrosive, inflammatory effects of the refluxed gastric contents and the vasovagal reflex. The regurgitated gastric acid can inflame and damage the pharyngeal and laryngeal mucosa, which are not protected against gastric acid exposure because of the absence of protective epithelial tissues, and cause a number of painful symptoms. The relaxation of the upper esophageal sphincter allows the backflow of acid-containing stomach contents, which irritates the delicate lining of the esophagus and triggers the vasovagal reflex, resulting in symptoms including cough and throating clearing [14]. Patients with OSAHS often suffer from LPRD, and much research has been conducted on the mechanism behind the concurrence of the two diseases [15]. However, there are few studies on the treatment regimen for both diseases. Therefore, this study explored the efficacy of pantoprazole, mosapride and domperidone for the treatment of OSAHS and LPRD.

Pantoprazole is an irreversible proton pump inhibitor, which is commonly used for the treatment of gastric and duodenal ulcers. It reduces the production of acid by blocking the proton pump, which is found within the parietal cells of the stomach and is the final step of acid production [16]. Pantoprazole enters parietal cells of the stomach wall and is activated by the gastric acid. It binds to proton pumps with high specificity, and prevents them from producing acid, thus lowering the acid levels in the stomach, and reducing the chances of gastric contents regurgitating to the throat. Pepsin secretion and activity are also inhibited in the process, thus reducing damage to the throat and number of swallows [17].

Mosapride, a gastroprokinetic agent, is mainly used to treat dyspepsia and reflux esophagitis [18]. Mosapride acts selectively on 5-hydroxytryptamine receptors in the myenteric plexus to stimulate the release of acetylcholine from cholinergic nerves, thus promoting gastric and duodenal motility and accelerating gastric emptying [19]. As a result, there will be few or no acidic contents in the stomach that can travel back up into the esophagus when patients' intra-abdominal pressure increase, thereby reducing the number of awakenings caused by foreign body sensation in the throat at night [20].

Domperidone, a peripheral dopamine receptor antagonist, can directly act on the gastric wall and increase lower esophageal sphincter pressure, thereby slowing down or preventing the backing up of gastric contents into the esophagus, and reducing the incidence of acid reflux [21]. Domperidone is also a gastroprokinetic agent. It can treat dyspepsia caused by gastroesophageal reflux, by facilitating gastric emptying, and preventing the reflux of gastric contents [22].

Intermittent snoring is a common symptom of OSAHS and indicates sleep apnea. Patients with OSAHS suffer from poor sleep because of the intermittent apneas, insufficient gas exchange in the lungs, and decreased oxygen supply to the brain during sleep [23]. Gas exchange abnormality caused by long-term apneas can cause lung damage, reducing lung capacities and lung volumes. It can also result in elevated carbon dioxide levels in the blood, and increased acidity of the body [24]. Patients with OSAHS often experience pauses in breathing during sleep. The blocked airway, the increased intratracheal pressure, the elevated intrapleural pressure, and the increased negative esophageal pressure may push gastric contents up.
Pantoprazole, mosapride and domperidone

The patient will then be awakened with a choking sensation, followed by a loud snoring as breathing resumes. This pattern can repeat many times a night. The patient’s laryngeal and pharyngeal muscles work harder to complete the swallowing process. This increased swallowing will compress the thoracic organs repeatedly, and cause a rise in the intrathoracic pressure, and a drop in the lung capacity, resulting in pulmonary dysfunction. The esophageal sphincter muscle will also be damaged in this process, increasing the incidence of LPRD.

Table 6. Comparison of severity LPRD and results of ABG between the two groups before and after treatment (n, %) (X ± sd)

<table>
<thead>
<tr>
<th></th>
<th>RSI&gt;13</th>
<th>RFS&gt;7</th>
<th>PaCO₂ (mmHg)</th>
<th>PaO₂ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (n=45)</td>
<td>40 (88.89)</td>
<td>41 (91.11)</td>
<td>45.93±10.81</td>
<td>54.56±13.37</td>
</tr>
<tr>
<td>Observation group (n=47)</td>
<td>43 (91.49)</td>
<td>45 (95.74)</td>
<td>46.14±11.33</td>
<td>53.26±13.32</td>
</tr>
<tr>
<td>χ²/t</td>
<td>0.184</td>
<td>0.813</td>
<td>0.091</td>
<td>0.467</td>
</tr>
<tr>
<td>P</td>
<td>0.674</td>
<td>0.368</td>
<td>0.928</td>
<td>0.642</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (n=45)</td>
<td>18 (40.00)*</td>
<td>20 (44.44)*</td>
<td>34.49±8.21*</td>
<td>66.88±16.82*</td>
</tr>
<tr>
<td>Observation group (n=47)</td>
<td>4 (8.51)*</td>
<td>4 (8.51)*</td>
<td>32.21±8.11*</td>
<td>71.32±17.83*</td>
</tr>
<tr>
<td>χ²/t</td>
<td>12.533</td>
<td>37.534</td>
<td>1.340</td>
<td>0.227</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.000</td>
<td>0.184</td>
<td>0.223</td>
</tr>
</tbody>
</table>

Note: *Compared with before treatment, p<0.05. LPRD, laryngopharyngeal reflux disease; ABG, arterial blood gas; RSI, reflux symptom index; RFS, reflux finding score; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide.

Figure 3. Comparison of severity LPRD of and AGB results between the two groups before and after treatment. A. Comparison of RSI and RFS scores between the two groups before and after treatment; B. Comparison of ABG results between the two groups before and after treatment. Compared with the control group, ***P<0.001; compared with pre-treatment between groups, *P<0.05. LPRD, laryngopharyngeal reflux disease; ABG, arterial blood gas; RSI, reflux symptom index; RFS, reflux finding score; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide.
awakenings were also reduced, thus improving patients' sleep quality.

Our study found that the proportion of patients whose RSI was above 13 and RFS above 7 in both groups decreased significantly after 8 weeks of treatment, and the drop was more noticeable in the observation group. The observation group also had significantly better pulmonary function parameters, lower proportion of stage I sleep, and higher proportion of stage III sleep than the control group. The API and AI for the observation group were significantly lower than those for the control group. Both groups showed improvements in the results of ABG analysis after treatment, but there was no statistically significant difference between the two groups.

These findings showed that pantoprazole blocked the final step of acid production, while domperidone increased the resistance of the retrograde flow of gastric contents. Mosapride and domperidone accelerated gastric emptying. The combination of these three drugs was effective in inhibiting gastric acid secretion, and reducing gastric contents, thereby alleviating or preventing acid reflux. Keeping acid reflux in check had the benefits of reducing the number of awakenings caused by foreign body sensation in the throat during sleep, and improving patients' quality of sleep. The frequency of swallowing and airway closure associated with it were also decreased, resulting in shorter duration of apneas, reduced number of apneas, improved lung function, reduced API and better pulmonary ventilation.

Our study also showed that the observation group had significantly higher total rate of effective treatment than the control group, proving the superior efficacy of the combined use of the three drugs. The reasons could be that the three drugs improved efficacy by their combined effects in treating acid reflux, and improving sleep quality, laryngeal mucosal inflammation and other clinical symptoms. The reasons for the statistically insignificant difference in the ABG results between the two groups could lie in the fact that the three drugs have limited effectiveness in significantly lowering acidity of the body caused by pulmonary gas exchange disorders. However, this is just a tentative analysis and is yet to be further confirmed.

In conclusion, pantoprazole combined with mosapride and domperidone can significantly improve lung function, sleep quality, and acid reflux symptoms for patients with OSAHS and LPRD.

Disclosure of conflict of interest

None.

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