Clinical efficacy and anti-recurrence effect of isatis root eye drops combined with ganciclovir eye drops in the treatment of Herpes simplex keratitis; a case report

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INTRODUCTION

Herpes simplex keratitis is one of the severest keratopathies with increasing incidence in recent years [1-3]. It refers to corneal inflammation caused by herpes simplex virus type I. Cellular and humoral immune responses are triggered on by infection with the virus. However, the virus ascends along the infected nerves and hides in trigeminal ganglion cells where conditions remain stable, and reactivate when the immune capability of the antibody decreases. Thus, this disease is associated with easy relapse. Clinical studies have found that without effective and timely treatment, herpes simplex keratitis may lead to increased recurrence or even risks of blindness [4–7]. Ganciclovir, a drug often used for the treatment of herpes simplex keratitis,
effectively inhibits virus growth, with satisfactory clinical outcomes. Modern Chinese medical research has revealed that although *isatis* root eye drop exerts obvious antiviral effect, it may stimulate burning and stinging pain sensations in patients, resulting in poor treatment compliance [8,9].

Therefore, this study investigated the clinical efficacy and recurrence-preventing effect of combination of *isatis* root eye drops and ganciclovir eye drops in treating herpes simplex keratitis.

**METHODS**

**General information**

Seventy-seven patients with herpes simplex keratitis in 81 eyes, who were admitted to our hospital between January 2018 and December 2019, were chosen and randomized into three groups: control group (CTG), combination group (CBG) and atomization group (AG), with 27 diseased eyes in each group. The patients comprised 43 males and 34 females aged 21-59 years. No notable differences in general information were observed among the three groups (p > 0.05).

**Inclusion criteria**

Patients who met the clinical diagnostic criteria for herpes simplex keratitis, and patients with complete clinical medical records were included in this study. The research obtained the approval of the ethics committee of The General Hospital of Tianjin Medicine University, Tianjin, China (approval no. 20171163), and was carried in line with the Declaration of Helsinki (as revised in 2013) [10]. The patients and their family members knew the purpose of the study, and they signed informed consent form.

**Exclusion criteria**

Patients with other eye diseases, patients who were allergic to the drugs used in the study, and those with cognitive disorders, were excluded from the study. Moreover, patients who were uncooperative during the study, those who took other anti-infective drugs within nearly one month prior to the study, and patients who were undergoing lactation or pregnancy, were excluded.

**Treatments**

Patients in CTG received ganciclovir eye drops (Hubei Everyday Bright Eyes Pharmaceutical Co. Ltd: specification: 8 mL; State Food and Drug Administration approval number: H20041429) at a dose of 1-2 drops 6 times daily. In CBG, patients were given *isatis* root eye drops (Chengdu Qingshan Likang Pharmaceutical Co. Ltd: specification: 8 mL; State Food and Drug Administration approval number: Z20090071) and ganciclovir eye drops alternately, 6 times daily, each at a dose of 1-2 drops. In AG, the patients were treated with ganciclovir eye drops 6 times a day, each at a dose of 1-2 drops. In addition, 30 mL of *isatis* root liquid medicine (4 mL of *isatis* root eye drops + 26 mL of purified water) was subjected to ultrasonic atomization for 15 min, and applied once a day.

**Evaluation of treatment indices**

**Treatment efficacy**

Patients were regarded as cured if the disease symptoms disappeared, with negative fluorescein staining, eyesight recovery and healed keratohelcosis. If the symptoms were relieved, and keratohelcosis was decreased, with decreased positive fluorescence staining range, the treatment was deemed to have improved the conditions of the patients. However, if the symptoms did not disappear, or if they were even worsened, the treatment was ineffective. Total treatment effectiveness (TE) was calculated as shown in Eq 1.

\[
TE (%) = \frac{(C + I)}{T} \times 100 
\]

where \( TE \) = total effectiveness; \( C \) = number of cured cases; \( I \) = number of improved cases; \( T \) = total number of patients.

The eyesight and the length of ulcer in all patients were determined before and after treatment, and their duration of treatment and the incidence of adverse reactions after treatment were recorded.

**Symptom scores**

Based on the herpesvirus keratitis symptom assessment scale designed by our hospital, the severity of patients’ symptoms was classified as nil, mild, moderate or severe, and these were scored 0, 1 point, 2 points and 3 points, respectively.

**Follow-up**

The patients were followed up for one year after treatment in order to record recurrence of disease.
Statistical analysis
The SPSS version 20.0 software was used for data processing, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for preparation of graphics. Measurement data are expressed as mean ± standard deviation (SD), and were statistically analyzed using t-test. Enumeration data are expressed as numbers and percentages [n (%)], and were analyzed using chi squared ($\chi^2$) test and normality test. Differences were statistically significant at $p < 0.05$.

RESULTS
Treatment effectiveness
The total treatment effectiveness was markedly higher in CBG and AG than in CTG ($\chi^2 = 4.9644, 6.8571, p = 0.026, 0.009$; Table 1).

Eyesight recovery/improvement
There was marked improvement in eyesight in each of the three groups after treatment, with better eyesight in CBG and AG than in CTG ($p < 0.05$; Figure 1).

Figure 1: Comparison of eyesight amongst the 3 groups. *$P < 0.05$, eyesight of the three groups before treatment vs eyesight of the three groups after treatment; **$p < 0.001$, eyesight of CBG after treatment vs eyesight of CTG after treatment; ***$p < 0.001$, eyesight of AG after treatment vs eyesight of CTG after treatment

Length of ulcer
After treatment, ulcer length was decreased in each of the three groups, with shorter length of ulcer in CBG and AG than in CTG ($p < 0.05$), and shorter length of ulcer in AG than in CBG ($p < 0.05$). These data are presented in Figure 2.

Figure 2: Comparison of the length of ulcer. *$P < 0.05$, length of ulcer in the three groups before treatment vs length of ulcer in the three groups after treatment; **$p < 0.001$, length of ulcer in CBG/AG after treatment vs length of ulcer in CTG after treatment; ***$p < 0.001$, length of ulcer in AG after treatment vs length of ulcer in CBG after treatment

Duration of treatment
The mean duration of treatment was shorter in CBG and AG than in CTG ($p < 0.05$). Moreover, CBG had shorter duration of treatment than AG ($p > 0.05$). These results are shown in Figure 3.

Symptom scores
Table 2 shows that there were decreases in symptom scores in the three groups after treatment ($p < 0.05$), but scores in CBG and AG were lower than score in CTG ($p < 0.05$).

Incidence of adverse reactions
As shown in Table 3, there were no marked differences in the incidence of adverse reactions among the three groups during the treatments ($p > 0.05$).

Incidence of disease recurrence
Recurrence incidence was lower in CBG and AG than in CTG ($p < 0.05$; Figure 4).

Table 1: Comparison of treatment effectiveness (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Ineffective</th>
<th>Improved</th>
<th>Cured</th>
<th>Total treatment effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG</td>
<td>10 (37.04)</td>
<td>8 (29.63)</td>
<td>9 (33.33)</td>
<td>17 (62.96)</td>
</tr>
<tr>
<td>CBG</td>
<td>3 (11.11)</td>
<td>9 (33.33)</td>
<td>15 (55.56)</td>
<td>24 (88.89) *</td>
</tr>
<tr>
<td>AG</td>
<td>2 (7.41)</td>
<td>8 (29.63)</td>
<td>17 (62.96)</td>
<td>25 (92.59) *</td>
</tr>
</tbody>
</table>

*$P < 0.05$, compared with CTG. Values are presented as [n (%)]
Figure 3: Comparison of the duration of treatment amongst the 3 groups. *P < 0.05, duration of treatment in CTG vs duration of treatment in CBG/AG

Table 2: Comparison of symptom scores (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG (n=27)</td>
<td>10.02±1.35</td>
<td>5.47±0.89</td>
<td>14.6215</td>
<td>0.000</td>
</tr>
<tr>
<td>CBG (n=27)</td>
<td>9.98±1.44</td>
<td>3.41±0.73*</td>
<td>21.1455</td>
<td>0.000</td>
</tr>
<tr>
<td>AG (n=27)</td>
<td>10.01±1.33</td>
<td>3.38±0.75*</td>
<td>22.5625</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P < 0.05

Table 3: Comparison of the incidence of adverse reactions

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTG (n=27)</th>
<th>CBG (n=27)</th>
<th>AG (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular itching and burning sensation</td>
<td>3 (11.11)</td>
<td>4 (14.81)</td>
<td>2 (7.41)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>3 (11.11)</td>
<td>2 (7.41)</td>
<td>3 (11.11)</td>
</tr>
<tr>
<td>Total incidence of adverse reactions</td>
<td>6 (22.22)</td>
<td>6 (22.22)</td>
<td>5 (18.52)</td>
</tr>
</tbody>
</table>

Table 4: Comparison of recurrence incidence among the three groups [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of recurrence cases</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTG (n=27)</td>
<td>11</td>
<td>40.74%</td>
</tr>
<tr>
<td>CBG (n=27)</td>
<td>2</td>
<td>7.41%*</td>
</tr>
<tr>
<td>AG (n=27)</td>
<td>1</td>
<td>3.70%**</td>
</tr>
</tbody>
</table>

*P < 0.05, recurrence in CTG vs recurrence in CBG; **P < 0.05, recurrence in CTG vs recurrence in AG.

DISCUSSION

Ultrasonic atomization destroys the tension and inertia on the surface of particle-free liquid medicine using ultrasonic wave. In this process, the liquid is reduced to less than 5-µm mist molecules which directly reach the lesions at enhanced drug concentrations, thereby reducing drug irritation, resulting in better therapeutic effect [11-14]. This method has been widely applied in the treatment of conjunctivitis, xerophthalmia and other eyelid diseases. Recent studies have found that isatis root exerted significant inhibitory effect on herpes simplex virus, and also enhanced the antibody function of tissue cells. The mechanism of its antiviral effect remains unclear, but its antiviral effect is caused by the synergistic action of multiple bioactive components.

At present, the main objective in the treatment of herpes simplex keratitis is to inhibit virus growth and reduce corneal injuries caused by repeated inflammation. Ganciclovir eye drops, when used alone for treating herpes simplex keratitis, produces rapid efficacy but it hardly results in radical elimination of the virus. Worse still, long-term repeated medication does not merely damage the cornea: it also results in gradual development of drug resistance, leading to increasing recurrence of disease and many adverse reactions [15-18]. In addition to ganciclovir eye drops, long duration of treatment with TCM alone is also associated with poor compliance in patients. Therefore, the treatment effectiveness of these two methods is still unsatisfactory. However, the combination of TCM with the aid of the technology of ultrasonic atomization has currently become the best method which effectively prolongs drug duration, reduces drug resistance and improves therapeutic effect [19].

In this study, total treatment effectiveness was higher in CBG and AG than in CTG. The eyesight of the patients in the three groups was improved after treatment, with better eyesight in CBG and AG than in CTG. Ulcer length was shortened in the three groups, with shorter ulcer length in CBG and AG than in CTG, and shorter length of ulcer in AG than in CBG. The duration of treatment in CBG and AG was shorter than that in CTG. Moreover, CBG had shorter duration of treatment than AG. The symptom scores in the three groups after treatment were decreased, with lower scores in CBG and AG than in CTG. Disease recurrence was lower in CBG and AG than in CTG. There were some similarities in results in CBG and AG, but treatment compliance in AG was higher, and there was no excessive stimulation during the whole process of treatment.

These results are consistent with those of Carter et al who reported that isatis root eye drops, whether aerosolized with ultrasound or used directly, exerted significant therapeutic effect when used in combination with ganciclovir eye drops in treating herpes simplex keratitis [20].
Limitations of the study

In this single-center study, the sample size of each group was relatively small. Therefore, there is a need for more multi-center studies with larger sample sizes to confirm the efficacy of the combination of *Isatis* root eye drops and ganciclovir eye drops in treating herpes simplex keratitis.

CONCLUSION

The use of combination of *Isatis* root eye drops and ganciclovir eye drops in the treatment of herpes simplex keratitis exerts significant therapeutic effects. The combined therapy lowers the duration of treatment, improves eyesight, and minimizes disease recurrence. Additional application of ultrasonic aerosolization further lowers the incidence of adverse reactions in patients, thereby providing a new direction for the clinical management of herpes simplex keratitis.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Liang Yin and Mingxue Zhang conceived and designed the study, and drafted the manuscript. Liang Yin, Mingxue Zhang and Hongguang Jin collected, analyzed and interpreted the experimental data. Liang Yin revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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14. McDonald EM, Patel DV, McGhee CN. A prospective study of the clinical characteristics of patients with


