Clinical efficacy of Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of oral submucous fibrosis and the effect on serum TGF-β1 and IL-6

Yan-Huan Zhao, Mei Xu, Yang Lu

Tangshan Union Medical College Hospital, Hebei, Tangshan 063000, China

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Objective: To explore the clinical efficacy of Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of oral submucous fibrosis (OSF) and the effect on serum TGF-β1 and IL-6. Methods: A total of 70 patients with OSF who were admitted in our hospital from October, 2015 to October, 2016 were included in the study and randomized into the observation group and the control group (n=35). The patients in the control group were given multipoint injection of triamcinolone acetonide (40 mg/time) in the basal region of oral mucosal regions. On this basis, the patients in the observation group were given additional Danshen injection (4 mL/time), 1 time/week, for 12 times. VAS was used for evaluation. The oral mucosa lesion area and mouth opening were measured. The morning fasting peripheral venous blood before and after treatment in the two groups was collected. The blood rheometer was used to detect the whole blood viscosity [high shear (HS), moderate shear (MS), and low shear (LS)], plasma viscosity (PV), and fibrinogen (FIB). ELISA was used to detect the serum TGF-β1 and IL-6 levels. Results: VAS score in the observation group was significantly reduced (P<0.05), mucosal lesion area was significantly less than that in the control group (P<0.05), and mouth opening was significantly greater than that in the control group (P<0.05). LS, MS, PV, and FIB after treatment in the observation group were significantly reduced when compared with before treatment (P<0.05), while LS, MS, HS, PV, and FIB after treatment in the control group were not significantly changed (P>0.05). TGF-β1 and IL-6 levels after treatment in the observation group were significantly lower than those in the control group (P<0.05). Conclusions: Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of OSF can effectively reduce the serum TGF-β1 and IL-6 levels, inhibit the connective tissue fibrosis, and improve the pain, oral mucosal lesion area, and mouth opening, with a satisfactory clinical effect.

1. Introduction

Oral submucous fibrosis (OSF) is a chronic and progressive oral mucosal disease with caneration tendency, and is characterized by reduced oral mucosal elasticity, pale and hardening oral mucosa, formation of submucosal fibrous bands, burning feeling of oral mucosa, progressive restriction of mouth opening, and tongue dyskinesia[1-2]. Eliminating or reducing the oral burning pain, and improving the oral mucosal stiffness and mouth opening restriction are mainly involved in the treatment of OSF[3]. Some researches demonstrate that Danshen injection in combined with glucocorticoids have a preferable effect on OSF[4]. The study was aimed to explore the clinical efficacy of Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of OSF and the effect on serum TGF-β1 and IL-6.
2. Materials and methods

2.1. General materials

A total of 70 patients with OSF who were admitted in our hospital from October, 2015 to October, 2016 were included in the study and randomized into the observation group and the control group with 35 cases in each group. All the patients were in accordance with the related diagnostic criteria of OSF \[5\]. Those who had general systemic disease and had taken immunoregulators in recent 3 months were excluded from the study. In the observation group, 21 were male, and 14 were female; aged from 20 to 62 years old; course from 1 to 8 years, with an average course of \((3.2 \pm 1.2)\) years. In the control group, 20 were male, and 15 were female; aged from 19 to 62 years old; course from 1 to 8 years, with an average course of \((3.2 \pm 1.3)\) years. The comparison of gender, age, and course between the two groups was not statistically significant \((P>0.05)\).

2.2. Methods

The patients in the control group were given multipoint injection of triamcinolone acetonide \((40mg/time)\) in the basal region of oral mucosal regions, 1 time/week, for 12 times. On this basis, the patients in the observation group were given additional Danshen injection \((4 mL/time)\), 1 time/week, for 12 times.

2.3. Observation indicators

VAS was used for evaluation, i.e. (1) no pain: 0 score; (2) mild pain: 1–2 scores; (3) moderate pain: 3–7 scores; (4) severe pain: 8–10 scores. The oral mucosa lesion area and mouth opening (distance between the incisal margin of superior and inferior central incisor) were measured. The morning fasting peripheral venous blood before and after treatment in the two groups was collected. The blood rheometer was used to detect the whole blood viscosity \([\text{high shear (HS), moderate shear (MS), and low shear (LS)}]\), plasma viscosity \((\text{PV})\), and fibrinogen \((\text{FIB})\). ELISA was used to detect the serum TGF-\(\beta\)1 and IL-6 levels.

2.4. Statistical analysis

SPSS 19.0 software was used for the statistical analysis. The measurement data were expressed as mean\(\pm SD\), and \(t\) test was used. Chi-square test was used for the enumeration data. \(P<0.05\) was regarded as statistically significant.

3. Results

3.1. Comparison of VAS score, mucosal lesion area, and mouth opening before and after treatment between the two groups

VAS score after treatment in the two groups was significantly reduced \((P<0.05)\), mucosal lesion area was significantly shrunk \((P<0.05)\), and mouth opening was significantly increased when compared with before treatment \((P<0.05)\). The mucosal lesion area after treatment in the observation group was significantly less than that in the control group \((P<0.05)\), while the mouth opening was significantly greater than that in the control group \((P<0.05)\) (Table 1).

3.2. Comparison of the hemorheology before and after treatment between the two groups

LS, MS, PV, and FIB after treatment in the observation group were significantly reduced when compared with before treatment \((P<0.05)\), but HS was not significantly changed \((P>0.05)\); while LS, MS, HS, PV, and FIB after treatment in the control group were not significantly changed when compared with before treatment \((P>0.05)\), and the comparison between the two groups was statistically significant \((P<0.05)\) (Table 2).

Table 1

Comparison of VAS score, mucosal lesion area, and mouth opening before and after treatment between the two groups \((n=35, \overline{x}\pm s)\).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>VAS score</th>
<th>Mucosal lesion area</th>
<th>Mouth opening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>Before</td>
<td>2.42\pm0.56</td>
<td>15.25\pm4.46</td>
<td>2.48\pm1.12</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>0.88\pm0.36'</td>
<td>7.56\pm2.31''</td>
<td>3.84\pm1.24''</td>
</tr>
<tr>
<td>Control</td>
<td>Before</td>
<td>2.38\pm0.71</td>
<td>15.21\pm4.52</td>
<td>2.75\pm1.17</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>0.91\pm0.42'</td>
<td>10.71\pm3.16''</td>
<td>2.75\pm1.14''</td>
</tr>
</tbody>
</table>

\(^*P<0.05\), when compared with before treatment; \(^#P<0.05\), when compared with the control group.

Table 2

Comparison of the hemorheology before and after treatment between the two groups \((n=35, \overline{x}\pm s)\).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Whole blood viscosity</th>
<th>PV</th>
<th>FIB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LS (\text{mg/L})</td>
<td>MS (\text{mg/L})</td>
<td>HS (\text{mg/L})</td>
</tr>
<tr>
<td>Observation</td>
<td>Before</td>
<td>14.57\pm1.83</td>
<td>9.51\pm0.98</td>
<td>5.36\pm0.48</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>8.76\pm1.23(^*)</td>
<td>5.20\pm0.57(^*)</td>
<td>5.13\pm0.34</td>
</tr>
<tr>
<td>Control</td>
<td>Before</td>
<td>14.54\pm1.76</td>
<td>9.48\pm0.95</td>
<td>5.35\pm0.51</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>13.75\pm1.73</td>
<td>8.97\pm0.74</td>
<td>5.11\pm0.55</td>
</tr>
</tbody>
</table>

\(^*P<0.05\), when compared with before treatment; \(^*P<0.05\), when compared with the control group.
3.3. Comparison of TGF-β1 and IL-6 levels before and after treatment between the two groups

TGF-β1 and IL-6 levels after treatment in the two groups were significantly reduced when compared with before treatment ($P<0.05$). TGF-β1 and IL-6 levels after treatment in the observation group were significantly lower than those in the control group ($P<0.05$) (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>TGF-β1</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>Before 7.56</td>
<td>26.76±7.56</td>
<td>25.75±8.24</td>
</tr>
<tr>
<td></td>
<td>After 8.92</td>
<td>7.89±3.15a</td>
<td>9.32±2.25a</td>
</tr>
<tr>
<td>Control</td>
<td>Before 7.56</td>
<td>25.76±7.64</td>
<td>25.43±8.37</td>
</tr>
<tr>
<td></td>
<td>After 5.28</td>
<td>15.32±5.28c</td>
<td>17.28±4.62c</td>
</tr>
</tbody>
</table>

* $P<0.05$, when compared with before treatment; ** $P<0.05$, when compared with the control group.

4. Discussion

The connective tissue collagen degeneration, collagen accumulation, epithelial atrophy, and vascular stenosis or occlusion are mainly involved in the pathological characteristics of OSF[6]. Some researches demonstrate that the connective tissue fibrosis is mainly associated with the inflammatory reaction, while the glucocorticoids posses the anti-inflammatory and immunosuppression effects, can significantly inhibit the release of various inflammatory mediators, regulate the inflammatory cell apoptosis, inhibit the proliferation of fibroblasts, and are the common drugs in the treatment of OSF[7]. Triamcinolone acetonide is the long-acting glucocorticoid, and play the anti-inflammatory and fibrosis inhibition effects for more lasting time, but long-term systemic application will cause the metabolic disorder, local mucosal atrophy, fungal infection, and other side effects[8]. Some researches demonstrate that microangiopathy is the main pathological characteristic of OSF[9]; therefore, blood circulation promoting to remove the blood stasis, and blood vessel expanding are of great significance in the treatment of OSF. The modern pharmacological researches show that Danshen can reduce the blood viscosity, decrease the platelet aggregation, eliminate the oxygen free radicals, expand the blood vessels, improve the microcirculation and hemorheology, inhibit the proliferation of fibroblasts, and promote the fibroblast apoptosis and collagen degradation, while local application can maintain the integrity of vascular endothelial cell membrane, and induce the formation of new capillaries. It is reported that hypercoagulation and fibrinolysis obstruction are mainly involved in patients with OSF, while Danshen can significantly decrease the blood FIB content, reduce the blood viscosity, improve the hemorheology, inhibit the proliferation of buccal mucosal fibroblasts and collagen synthesis, and improve the clinical symptoms[10]. It is reported that adoption of prednisone in combined with Danshen injection in the treatment of middle and advanced OSF can significantly improve the mouth opening degree and mucosal lesion area after 3 months, while the mouth opening degree and mucosal lesion area are not significantly improved in patients treated by pure prednisone[11]; therefore, it is argued that pure hormone can reduce the inflammatory reaction, but can not resolve the microvascular stenosis and occlusion. The results in the study showed that VAS score in the observation group was significantly reduced ($P<0.05$), mucosal lesion area was significantly less than that in the control group ($P<0.05$), and mouth opening was significantly greater than that in the control group ($P<0.05$); LS, MS, PV, and FIB after treatment in the observation group were significantly reduced when compared with before treatment ($P<0.05$), while LS, MS, HS, PV, and FIB after treatment in the control group were not significantly changed ($P>0.05$), indicating that Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of OSF can effectively inhibit the connective tissue fibrosis, and improve the hemorheology, with a significantly effect superior to that by pure hormone.

TGF-β1 is involved in various histocyte activity and pathophysiologic process, promote the cell differentiation and fibroblast chemotaxis, inhibit the proliferation of epithelial cells, is involved in the immune response, promote the angiogenesis, change the cell adhesion function, and is one of the most important pro-fibrosis cytokines for the occurrence and development of various fibrotic diseases[12,13]. IL-6 has a multifunctionality, can induce the maturation of T and B cells, mediate the acute inflammatory reaction, inhibit the decomposition of extracellular matrix, promote the proliferation of fibroblasts, increase the collagen aggregation, and promote the formation of fibrosis[14]. Some researches demonstrate that triamcinolone acetonide has a stronger anti-inflammatory effect, can promote the synthesis of immunoglobulin, and inhibit T cell activity to reduce the inflammatory reaction, while Danshen can induce the fibroblast apoptosis to facilitate the ultrastructures of fibroblasts, epithelial cells, and endothelial cells reach the normal cell level, and promote the degradation and absorption of collagen fiber to reach the anti-fibrosis effect in order to effectively reduce the serum IL-6 and TGF-β1 levels[15,16]. The results in the study showed that TGF-β1 and IL-6 levels after treatment in the observation group were significantly lower than those in the control group ($P<0.05$), indicating that Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of OSF have a preferable anti-fibrosis and anti-inflammatory effects.

In conclusion, Danshen injection in combined with local injection of triamcinolone acetonide in the treatment of OSF can effectively reduce the serum TGF-β1 and IL-6 levels, inhibit the connective
tissue fibrosis, and improve the pain, oral mucosal lesion area, and mouth opening, with a satisfactory clinical effect.

References


