Study on the clinical effect and safety of Kangfuxin liquid combined with microneedling in the treatment of facial skin photoaging

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Author contributions
Yi Chen, Ting-Ting Zhong, Rui-Lan Xi and Dan Xiao designed the paper; Yi Chen and Yan Wang wrote the manuscript; Hu Ren, Qiong Guo and Yan Wang guided the paper; Yi Chen, Ting-Ting Zhong, Rui-Lan Xi, Dan Xiao and Yan Wang collected the data. All authors have read and agreed to the final draft.

Competing interests
The authors declare no conflicts of interest.

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Abstract
Background and Objectives: Microneedling has been introduced as a new technique to address the growing concern of facial skin photoaging. Kangfuxin liquid has been found to promote the process of skin wound repair, including reducing inflammatory response, improving immunity and enhancing antioxidant levels. In this prospective randomized double-blinded study, we wanted to explore the clinical efficacy and safety of Kangfuxin liquid combined with microneedling in treating facial skin photoaging.

Methods: 57 patients with facial skin photoaging were randomly divided into two groups. The treatment group (28 cases) received microneedle therapy with Kangfuxin liquid, while the control group (29 cases) received microneedle therapy with physiological saline. The treatment interval was 4 weeks, and a total of 3 treatments were performed. Compare the VISIA scores of facial photoaging features such as wrinkles, texture, pores, spots and ultraviolet pigmentation between two groups of patients before and after treatment, Global Score for Photoaging, satisfaction evaluation, and record the occurrence of adverse reactions.

Results: After treatment, the treatment group showed more significant improvement in wrinkles, texture, pores, spots and ultraviolet pigmentation, and the Global Score for Photoaging was better than the control group (P < 0.05). The satisfaction rate with improving skin in the treatment group was 85.71%, which was higher than 75.86% in the control group (P < 0.05). Both groups did not experience adverse reactions such as skin infection, pigmentation or hypopigmentation, scar formation, or worsening of melasma.

Conclusion: Kangfuxin liquid combined with microneedling therapy has a good improvement effect on facial skin photoaging, with a low incidence of adverse reactions and high patient satisfaction. It is worthy of clinical promotion.

Keywords: Kangfuxin liquid; microneedling; facial skin photoaging; VISIA
Background

Skin aging is influenced by internal and external factors of the body, among which ultraviolet (UV) is an important external cause of skin aging, and the skin aging caused by UV is called photoaging [1]. The histological manifestations of skin photoaging include reduced collagen content, elastic fiber degeneration and lipid peroxide deposition. The clinical manifestations include premature skin wrinkles, skin laxity, pigmentation, telangiectasia, etc. [2]. More seriously, skin photoaging can induce malignant skin tumors [2].

Currently, multiple methods are applied to improve facial skin photoaging, such as chemical peeling, intense pulsed light, laser, radiofrequency, injection and filling, plastic surgery, etc. However, these methods have adverse reactions such as high treatment cost, postoperative pigmentation or hypopigmentation, persistent erythematosis, scar and melasma exacerbation [3]. Exfoliative laser is considered the gold standard for improving facial skin photoaging, but its application is limited by the increased risk of pigmentation in the yellow race [4]. Research has found that microneedling can promote collagen regeneration and remodeling, promote the synthesis of extracellular matrix in the epidermis and dermis, regulate epidermal melanin metabolism and improve the symptoms of photoaging such as wrinkles, rough texture, and enlarged pores [5]. Kangfuxin liquid can promote the process of skin wound repair, including reducing inflammatory response, improving immunity and enhancing antioxidant levels. Therefore, we aimed to investigate a safer, more effective and more economical method. In this study, we utilized Kangfuxin liquid in combination with microneedling to treat facial skin photoaging and achieved favorable therapeutic effects. The following report presents our findings.

Materials and methods

We conducted a prospective, randomized, double-blinded study involving 57 patients with facial skin photoaging to evaluate the efficacy and safety of combining Kangfuxin liquid with microneedling. The study protocol adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki and was approved by our Institutional Medical Ethics and Human Research Committee (Approval No: 2021091001). Prior to their participation in the study, all patients were provided with detailed information regarding the treatment, including potential risks, benefits and possible complications. Informed consent was obtained from each patient before their enrollment in the study.

Study participants

Because women are more concerned about the issue of facial skin photoaging, all patients seeking treatment based on facial photoaging are women aged 30–70. Fifty-seven Chinese women (Fitzpatrick II–IV) with photaging signs on the face were recruited from the out-patient clinic in Department of Medical Cosmetology, The First Affiliated Hospital of Dal University. Diagnostic criteria refer to the “Glogau Grading Standards for Photoaging [6]”, which meets the diagnosis of moderate to severe photoaging as grade II–III. The clinical manifestations include more static lines visible on the face, uneven skin color with more spots, skin keratinization, and roughness limited to a few areas of the skin. Participants aged 30–70 years with moderate to severe facial skin photoaging were enrolled, and they provided written informed consent before inclusion. Exclusion criteria included retinoid use within the previous 6 months, pregnancy, normal blood coagulation or taking anticoagulants; history of keloid formation; allergy to the study drug; and poor treatment compliance.

Treatment protocols

Fifty-seven patients were divided into the treatment group and the control group according to random number table method. The treatment group (28 cases) was aged: 35–68 years old, average age: 52.71 ± 9.10 years old and an average course of disease: 10 ± 7.64 years; the control group (29 cases) age: 36–67 years old, mean age: 52.45 ± 8.18 years old, mean course of disease: 10 ± 7.85 years.

There were no significant differences in age, course of disease, overall degree of photoaging and VISIA scores of wrinkles, textures, pores, spots and UV pigmentation in the two groups (all P > 0.05), indicating comparability.

Apply 20 g of compound lidocaine cream on the patient’s face (Tongfang Pharmaceutical Group Co., Ltd., NO: H20063466, Beijing, China) on the patient’s face, seal for 40 minutes and disinfect the skin. The experimenter selects the microneedle size based on the patient’s skin photoaging characteristics. For those with thin skin or accompanied by melasma, a needle length of 0.5–1 mm is selected, while for those with wrinkles or large pores, a needle length of 1.0–1.5 mm is selected. The microneedle is rolled across the face. During the rolling process, 50 ml of physiological saline was introduced into the control group, while the treatment group received the same dose of Kangfuxin liquid. Treatment endpoint: patients with thin skin or accompanied by melasma have needle-like bleeding or skin flushing, while those with wrinkles and large pores have patchy bleeding as the treatment endpoint. The duration and frequency of wet compress with Kangfuxin liquid/physiological saline in the treatment group/control group after surgery are the same, with a duration of 3 days, 20 minutes each time, 2 times per day.

Observation indicators

Clinical efficacy. Before each treatment, the changes in wrinkle, texture, pores, spots and UV pigmentation scores of the two groups of patients were recorded using the VISIA measuring instrument (Canfield Company, Model Generation 7, Maine, America). This instrument provided objective measurements for these parameters. Additionally, prior to treatment and 12 weeks after the first treatment, two dermatologists who were not involved in the experiment evaluated the overall degree of photoaging in the patients based on their photographs. They used the Global Score for Photoaging (GSP) [7] to assess the clinical efficacy of the treatment.

Satisfaction evaluation. Record the patient’s evaluation of the improvement in skin (including skin tone and skin smoothness) after treatment, which is divided into 4 levels. Level 0 is unsatisfactory, level 1 is slightly satisfactory, level 2 is satisfactory and level 3 is very satisfactory. The total satisfaction rate is the percentage of the total number of patients at level 2 and level 3 combined.

Safety evaluation. Record the occurrence, severity and duration of adverse reactions such as erythema, swelling, burning, subcutaneous ecchymosis, pigmentation or hypopigmentation, infection and scars.

Statistical analysis

The collected data were analyzed using SPSS software (version 26.0; IBM, Armonk, NY, USA). For normally distributed data, analysis of variance and student’s t-test were employed. Nonparametric statistical methods, such as the Kruskal-Wallis test and Mann-Whitney test, were utilized for data with skewed distributions. A P-value less than 0.05 was considered statistically significant.

Results

Clinical efficacy

After three treatments, the wrinkles, texture, pores and UV pigmentation of the two groups of patients were improved, and GSP decreased compared to before, with statistically significant differences (P < 0.05). However, the treatment group showed better improvement in texture, pores, and UV pigmentation than the control group, with GSP lower than the control group, and the difference was statistically significant (P < 0.05) (Table 1, Table 2).

Satisfaction evaluation

The satisfaction rate of the treatment group in improving skin photoaging was 85.71%, while the control group was 75.86%, with a statistically significant difference (Z = 1.997, P < 0.05) (Table 3).
Safety evaluation
All patients experienced flushing, mild edema and partial purpura on their facial skin after surgery, accompanied by a burning sensation. They all resolved spontaneously within 3–5 days. All patients did not experience adverse reactions such as post-inflammation pigmentation or hypopigmentation, scarring, or worsening of melasma (Figure 1).

Discussion
Skin photoaging is characterized by various skin changes, including the presence of wrinkles, skin laxity, rough texture, irregular pigmentation, telangiectasia and hyperkeratosis. In severe cases, it can even lead to the development of skin malignant tumors [8]. The effects of skin aging extend beyond mere aesthetic concerns and can also impact overall human health. The process of photoaging primarily involves oxidative stress, inflammatory reactions, apoptosis and collagen degradation, among other factors. Exposure to UV radiation triggers the production of excessive reactive oxygen species, which subsequently activate nuclear factor-κB and the mitogen-activated protein kinase signaling pathway. This activation, in turn, upregulates the expression of matrix metalloproteinases. It leads to the degradation of collagen, elastin and other connective tissues in the extracellular matrix [9]. UV irradiation can promote the synthesis and release of various inflammatory mediators and induces

<table>
<thead>
<tr>
<th>VISIA measurement value</th>
<th>Group</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrinkles</td>
<td>Treatment</td>
<td>50.07 ± 6.41</td>
<td>51.04 ± 8.91</td>
<td>54.68 ± 7.51</td>
<td>55.68 ± 8.86</td>
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<td>Control</td>
<td>50.67 ± 7.92</td>
<td>51.69 ± 7.92</td>
<td>54.48 ± 8.70</td>
<td>55.10 ± 8.48</td>
</tr>
<tr>
<td>Texture</td>
<td>Treatment</td>
<td>51.82 ± 5.93</td>
<td>53.75 ± 5.55</td>
<td>56.79 ± 5.69</td>
<td>60.25 ± 6.37*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>51.62 ± 5.73</td>
<td>53.96 ± 5.69</td>
<td>55.62 ± 5.77</td>
<td>57.90 ± 4.47</td>
</tr>
<tr>
<td>Pores</td>
<td>Treatment</td>
<td>61.14 ± 4.41</td>
<td>65.39 ± 4.68*</td>
<td>66.79 ± 4.21*</td>
<td>69.93 ± 3.59*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>61.07 ± 4.01</td>
<td>63.79 ± 5.37*</td>
<td>65.31 ± 4.66</td>
<td>67.45 ± 4.71*</td>
</tr>
<tr>
<td>Spots</td>
<td>Treatment</td>
<td>47.46 ± 8.27</td>
<td>47.85 ± 7.76</td>
<td>48.89 ± 7.20</td>
<td>49.10 ± 8.17</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>47.37 ± 8.64</td>
<td>47.79 ± 6.86</td>
<td>48.17 ± 7.76</td>
<td>49.00 ± 8.96</td>
</tr>
<tr>
<td>UV pigmentation</td>
<td>Treatment</td>
<td>44.79 ± 8.17</td>
<td>48.92 ± 5.21*</td>
<td>51.07 ± 7.53*</td>
<td>53.82 ± 5.89*</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>44.93 ± 8.59</td>
<td>45.79 ± 6.28</td>
<td>48.14 ± 5.48*</td>
<td>50.55 ± 6.00*</td>
</tr>
</tbody>
</table>

*, there is a statistically significant difference between the same group after treatment and baseline, P < 0.05; #, there was a statistically significant difference between the two groups after treatment, P < 0.05. UV, ultraviolet.

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>3.0(1.0)</td>
<td>2.0(1.0)</td>
<td>3.928</td>
<td>0.000</td>
</tr>
<tr>
<td>Control group</td>
<td>3.0(1.0)</td>
<td>2.5(1.0)</td>
<td>2.364</td>
<td>0.018</td>
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<tr>
<td>Z</td>
<td>0.323</td>
<td>2.490</td>
<td></td>
<td></td>
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<tr>
<td>P</td>
<td>0.747</td>
<td>0.013</td>
<td></td>
<td></td>
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</tbody>
</table>

GSP, Global Score for Photoaging.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Level 0</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Overall satisfaction rate</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>28</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>18</td>
<td>85.71%</td>
<td>1.997</td>
<td>0.040</td>
</tr>
<tr>
<td>Control group</td>
<td>29</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>10</td>
<td>75.86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Comparison of VISIA scores before and after treatment (x ± s)

Table 2 Comparison of GSP scores before and after M (Q)

Table 3 Patient satisfaction evaluation form n (%)

Figure 1 Typical cases before and after facial photoaging treatment. A–A4, before treatment wrinkles, texture, pores, spots, UV spots; B–B4, front wrinkles, texture, pores, spots, UV pigmentation after 3 treatment. UV, ultraviolet.

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phosphorylation of extracellular regulated protein kinase pathways to produce pro-inflammatory cytokines such as IL-α, IL-1, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor. It also triggers inflammatory cell infiltration, resulting in the degradation of matrix collagen and the destruction of elastic fibers [10]. These factors cause irregular atrophy or hypertrophy of the skin, reduction or increase of melanocytes, reduction of Langerhans cells, and significant thinning of the dermis, reduction of type I collagen fibers, degeneration of elastic fibers and tortuous dilation of blood vessels, which are characteristic histological changes of photoaging [11]. Therefore, how to promote collagen regeneration, reduce oxidative reaction and inflammatory damage is the focus of improving photoaged skin.

Microneedling can promote collagen regeneration and remodeling, promote the synthesis of extracellular matrix in the epidermis and dermis, improve the symptoms of photoaging such as wrinkles, rough texture and enlarged pores, and regulate epidermal melanin metabolism [5]. Multiple dot-matrix injuries formed by microneedles on the skin surface enable the wound to establish a healing cascade and release multiple cytokines such as transfer growth factor, fibroblast growth factor, platelet-derived growth factor, connective tissue activating protein and connective tissue growth factor. Various cytokines act on keratinocytes and fibroblasts [12] to promote local angiogenesis and collagen synthesis [11]. Furthermore, microneedles have the ability to activate the Na+K+ p-pump, leading to the formation of an electromagnetic mixed field. This activation significantly enhances cell activity, induces collagen regeneration and remodeling, and creates several reversible microchannels in a minimally invasive manner. These microchannels allow for the direct delivery of drugs into the dermal blood vessels, thereby greatly improving the drug's permeability [13].

Kangfuxin liquid is a crude extract of Periplaneta Americana, extracted by a mixture of ethanol and water solvent. The active ingredient is peptides, with a content of 70% to 90%. The Periplaneta Americana was originally published in the Shennong's Classic of Materia Medica (unknown author, 25–220 C.E.), used to treat blood stasis, cold heat, broken accumulation, throat arthralgia, internal cold chillness and other symptoms. Later, it was found to have a good repairing effect on skin trauma, ulcers, pressure sores, etc.; it was widely used in tissue injury healing and inflammatory repair [14]. Domestic and foreign studies have found that Periplaneta Americana can promote the process of skin wound repair, including reducing inflammatory response, improving immunity and enhancing antioxidant levels [15]. Liu Rongrong et al. [16] found that Kangfuxin liquid can achieve the effect of wound repair by promoting the proliferation of fibroblasts. Kangfuxin liquid could promote the proliferation of fibroblasts in a time-dependent manner at the concentration of 3–100 µg/mL, and the effect was the strongest at 48 and 72 hours. Kangfuxin liquid also has functions similar to epidermal growth factor and basic fibroblast growth factor, activating immune cells during the inflammatory phase and accelerating body repair [17]. Kangfuxin liquid has multiple effects as anti-inflammatory, antioxidant, immune regulation and promoting wound healing.

Therefore, in this study, we employed a combination therapy involving Kangfuxin liquid and microneedling for the treatment of facial skin photoaging. Following three treatment sessions, both the treatment group and the control group exhibited improvements in wrinkles, texture, pores, and UV pigmentation compared to their initial conditions and GSP decreased. However, the improvement degree of GSP in the experimental group was better than that in the control group, and the scores of texture, pores, and UV pigmentation in the experimental group were higher than those in the control group. The possible reason for this may be that Kangfuxin liquid has been shown to reduce inflammatory reactions, enhance the body's immune system, and increase antioxidant levels. A study by Wang Xiong et al. [18] reported that Kangfuxin liquid can resist the damage of ultraviolet radiation B to immortalize human epidermal keratinocytes, protect their cell membrane integrity, and achieve the effect of resisting skin photoaging. At the cellular level, Kangfuxin liquid has been found to upregulate the expression of cytokines such as transforming growth factor, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor and tumor necrosis factor [19, 20], which play crucial roles in skin repair processes. This combined treatment approach promotes collagen regeneration, reduces oxidative reactions, mitigates inflammatory damage, and improves skin symptoms associated with photoaging. Consequently, it enhances the overall effectiveness of clinical treatment and increases patient satisfaction. Notably, none of the patients in the study experienced adverse reactions such as post-inflammatory pigmentation or hypopigmentation, scarring, or worsening of melasma, indicating the safety and tolerability of the treatment.

Conclusion

The combination therapy of Kangfuxin liquid and microneedling has shown a significant therapeutic effect on facial skin photoaging. This treatment approach not only yields positive results in improving various aspects of photoaging but also demonstrates a low incidence of adverse reactions and high patient satisfaction. Based on these findings, it can be concluded that the combination of Kangfuxin liquid and microneedling is an effective and well-tolerated treatment method for facial skin photoaging.

References


