ORIGINAL ARTICLE

A Study on the Alterations in Skin Viscoelasticity before and after an Intradermal Administration of Growth Factor

Background: While photo-aging is believed to be preventable by the complete blockage of ultraviolet rays, there is no epoch-making method except sing fillers or autologous fat injection, for rejuvenating the skin once it has aged. **Objective:** Our group developed a new method for rejuvenating aged skin by the direct intradermal injection of basic fibroblast growth factor, the first method of its kind in the world. In this paper we report the results of long-term follow-up observations and alterations in skin viscoelasticity before and after this treatment. **Materials and Methods:** A single dose of growth factor was injected directly into aged skin of the dorsal surface of the hand intradermally. The skin viscoelasticity of 50 treated cases was measured by a cutometer just before the treatment and at 1, 3, 6, and 9 months after treatment, respectively. **Results:** We observed the following rejuvenating effects: improved skin softness, gradual improvement of turgor, improved thickness of atrophied skin, and greatly improved viscoelasticity which reveals the improvement of biomechanical properties of the treated aged skin. According to the comparisons of viscoelasticity between pre- and post-treatment, the rejuvenated changes of R2 and R7 values were comparable to an age difference of more than 20 years. **Conclusion:** This method was confirmed to have excellent effects in rejuvenating aged skin safely and reliably including biomechanical properties. With this advance, we expect conventional non-physiological skin rejuvenating treatments to be replaced by a much more fundamental method using one-time injections of the growth factor.

KEYWORDS: Anti-aging, biomechanical property, growth factor, photo--aging, rejuvenation, viscoelasticity

INTRODUCTION

When the skin is exposed to ultraviolet (UV) rays over a long-period of time, the photo-aging phenomenon advances. The process visibly ages the skin of the face.[1-3] and the back of the hands [Figure 1]. While photo-aging is thought to be preventable by a complete blockage of UV rays,[4] there is no epoch-making method for rejuvenating the skin once it has aged.[3,4] Treatments with fillers,[5-9] botulinus toxin injections,[10] autologous fat injection or lasers and intensive pulsed light[11] are ancillary and confer only temporary effects that wear off without repetitive, continuous treatment.[6]

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MATERIALS AND METHODS

Our group developed a method for rejuvenating the skin by administering a growth factor directly into the dermal portion of aged skin. The effective agent in the test solution was a commercially available growth-factor preparation delivered as a spray (basic fibroblast growth factor (bFGF): Fibrast Spray™, Kaken Pharma. Co., Tokyo, Japan).[12-14] The preparation has been available, in spray form only, since 2001, when it was approved as an ulcer treatment by the Ministry of Health, Labor and Welfare in Japan. On November 23, 2007, after approval was obtained from the ethic committee for clinical studies of the Sapporo Medical University Hospital, a investigator-initiated clinical study was commenced to investigate whether or not the growth factor injected directly to a skin region with UV-induced photo-aging and atrophy would alleviate the conditions. To date, 185 hands (115 dorsal surfaces of right hands and 70 dorsal surfaces of left hands) of 126 subjects have been treated. A total of 193 injections have been administered to subjects with a mean age of 54.2 years. Before each treatment, the

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Figure 1: When the dorsal surface of the hand skin is aged due to natural aging or exposure to UV rays, age-related conditions of the skin such as atrophy, reduced viscoelasticity, protuberant blood vessels, and see-through tendon tissue progress.

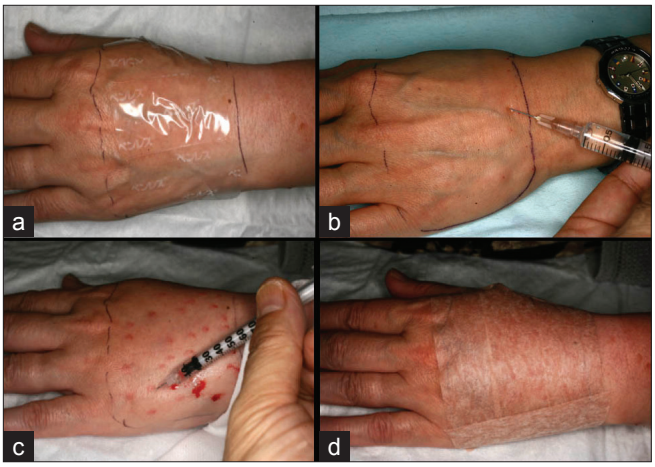

Figure 2: Practice of the treatment. (a) Preparation with Xylocaine-treated tape. (b,c) A single dose of the infused test solution was administered at 0.2 ml/cm^2. (d) After the treatment, the treated area was covered with adhesive tape.

researcher and the patient observed the dorsal surfaces of both hands, and the side exhibiting stronger aging symptoms was treated first.

The treatment agent, bFGF, was adjusted to a concentration of 10 µg. For storage and treatment, the test solution was taken up directly into a 1 ml insulin syringe integrated with a 29G needle (BD Plastipack 326611, Becton, Dickinson and Company Japan, Fukushima, Japan) on a clean bench placed in an air clean room. Immediately after preparation, the divided solution was stored in a deep freezer at −80°C. The frozen solution was defrosted just before use and infused directly to the treated site. In the current clinical trial, a test solution prepared according to the above-described procedures was infused directly into the dermis of atrophic, UV-damaged skin under local anaesthesia. The infusion volume of the test solution per treatment was set at 0.2 ml (2 µg for bFGF) per cm^2 of lesion, and the maximum total volume was set at 5 ml (50 µg FGF in total) for a single treatment session. This dose enabled the delivery of a single dose to almost the whole dorsal surface of the unilateral hand. After the treatment, the whole treated area was covered with adhesive tape [Figure 2a-d]. Because the treatment of administrating the growth factor was experimental, as a rule, the analyses were only conducted for cases treated with a single dose of the test solution. In cases where senile-pigmented macules were present at the treated site, the treatment was combined with irradiation by a long-pulse Alexandrite laser (Gentle LASE LE, Candela, Boston, MA, USA) in the confined regions of skin where the pigmented macules were observed, followed by topical application of a 4% hydroquinone ointment. Overall, 34% of the patients received partial laser irradiation. Following the treatment, the subjects were advised to completely shield the treated area from UV rays using a SPF 50+ sunscreen cream (2e, Maruho Co., Ltd. Osaka, Japan), to take vitamin C orally (Cinal, Shionogi & Co., Ltd., Tokyo, Japan), and to quit smoking.

Skin viscoelasticity determined by cutometer

A cutometer (Cutometer MPA 580, Courage & Khazaka Electronic GmbH, Cologne, Germany)[15,16] was used to measure the viscoelasticity, the biomechanical property of the skin just before the single dose of the test solution was injected and at 1, 3, 6 and 9 months after injection, in 50 treated cases. In brief, the measured skin was sucked up with a 2-second suction negative pressure at 300 mbar using a hand-piece with a suction pore of 2 mm in diameter, and released. The ratios of the displacement at 0.1 (Ur) and 2 seconds (R8=Ua) after the release to the displacement degree (R0=Uf) and keep-up were determined. The ratios R2=Ua/Uf and R7=Ur/Uf were recorded and analysed.

Before this comparison, the R2 and R7 values of 230 females in age groups from 10 to 90 years old (grouped by decade, 30 hands in each group) were measured and the normal alterations of skin viscoelasticity on the dorsal surface of the hand with aging were elucidated. Two sites on the dorsal surface were measured and the mean value was used for the analysis. The correlation between the viscoelasticity (R2, R7) and age was determined by regression multi-nominal analyses.

The viscoelasticity measured at 1, 3, 6 and 9 months after treatment was compared in the 50 hands treated[9] or more months earlier. Next, using the regression curve calculation formula for normal groups, the age

corresponding to the measured skin viscoelasticity was determined and the treatment effect was evaluated by comparing the pre-treatment values with the values at 1, 3, 6 and 9 months after treatment.

Statistical analysis

Statistical analysis was performed by analysis of variance (ANOVA) followed by Fisher's comparison test and regression multi-nominal analyses using Statview-J 4.02 (Abacus Concepts Inc., Berkley, CA, USA).

RESULTS

The clinical trial of this therapy with long-term follow-up demonstrated excellent rejuvenating effects on the dorsal surface of the hand. The rejuvenation observed was comparable to that observed in an earlier study with a short-term follow-up[13] assessing the skin of the hands and face.[12,14] Specifically, a single intra-dermal administration of the test solution gradually improved the softness and turgor of the skin, thickened atrophic skin, and concealed protuberant vessels and see-through tendinous tissue in almost all of the treated cases. The rejuvenating effect progressed over time after the single treatment and lasted for 2 years or longer. Swelling of the skin was observed just after the treatment, but had fully subsided by the end of the second post-treatment week. Thereafter, the rejuvenating effect progressed gradually up to 6-9 months and was retained for 2 years or more. The effects were observed in all of the treated cases and there were no major harmful events except purpura of the treated site. As indicated, sufficient effects were elicited by only one local injection of bFGF.

Skin viscoelasticity measured by cutometer

The viscoelasticity of the skin in the normal age-groups was determined by the cutometer before the treatment, and the results indicated an age-dependent decrease of skin viscoelasticity. The correlations of R2 and R7 values with age were as follows: (R2) = 1.129 – 0.007 × (age) + 8.975 × 10^{-6} × (age)^2 (correlation coefficient R=0.783) [Figure 3]; (R7)=1.194 – 0.019 × (age) + 1.006 × 10^{-4} × (age)^2 (correlation coefficient R=0.812) [Figure 4]. Based on the normal variations in the dorsal surface of the hands, skin viscoelasticity was investigated before and after the growth factor treatment. The R2 value (post-2-second return rate) changed from 0.7289 ± 0.0670% (corresponding to an age of 61.23 years) before treatment to 0.8590 ± 0.0698 (corresponding to an age of 44.13 years) (P<0.0001) at 1 month post-treatment, 0.8842 ± 0.0448 (corresponding to an age of 40.24 years) (P<0.0001) at 3 months post-treatment, 0.8898 ± 0.0642 (corresponding to an age of 37.90 years) (P<0.0001) at 6 months post-treatment, and 0.9183 ± 0.0418 (corresponding to an age of 39.66 years) at 9 months post-treatment. Overall, the results indicate statistically significant rejuvenating effects corresponding to an age difference of 20 years or more (P<0.0001) [Figure 5]. Compared to the R2 values obtained at 1 month after treatment, the values obtained at 3 (P<0.05), 6 (P<0.01) and 9 months (P<0.0001) after treatment were significantly higher. R7, a value believed to represent the immediate elasticity (post-0.1-second return rate), changed from 0.4288 ± 0.908% (corresponding to an age of 57.80 years) before treatment to 0.5879 ± 0.1043 (corresponding to an age of 43.21 years) (P<0.0001) at 1 month post-treatment, 0.6131 ± 0.0952 (corresponding to an age of 41.08 years) (P<0.0001) at 3 months post-treatment, 0.6830 ± 0.0903 (corresponding to an age of 35.46 years) (P<0.0001) at 6 months post-treatment, and 0.7116 ± 0.0807 (corresponding to an age of 33.27 years) at 9 months post-treatment. These variations also indicate rejuvenating effects corresponding to an age difference of 20 years or more (P<0.0001) [Figure 6].

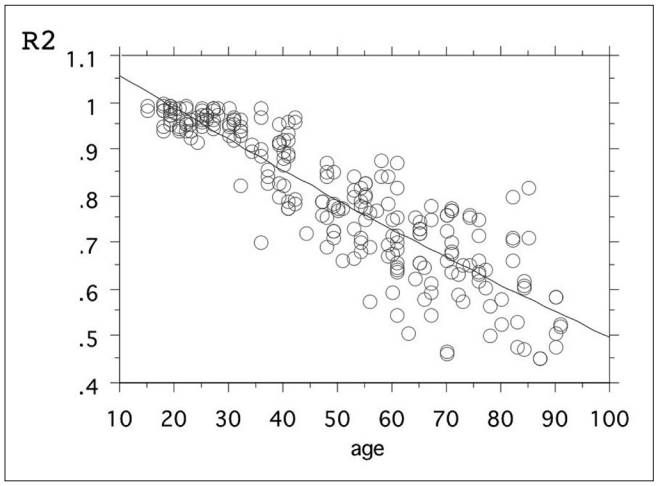

Figure 3: Correlation between the R2 value and age in normal age groups

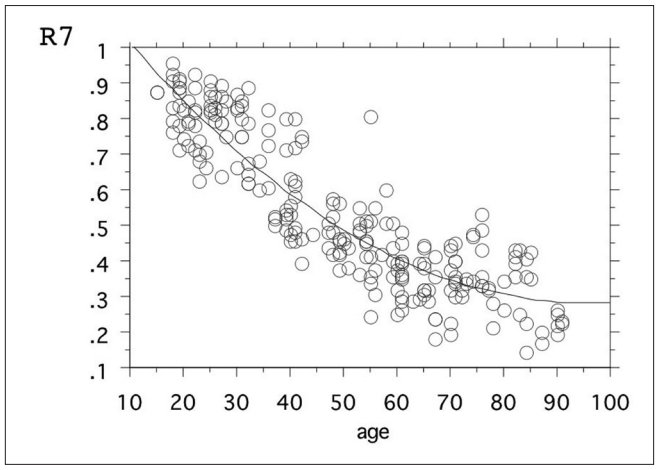

Figure 4: Correlation between the R7 value and age in normal age groups

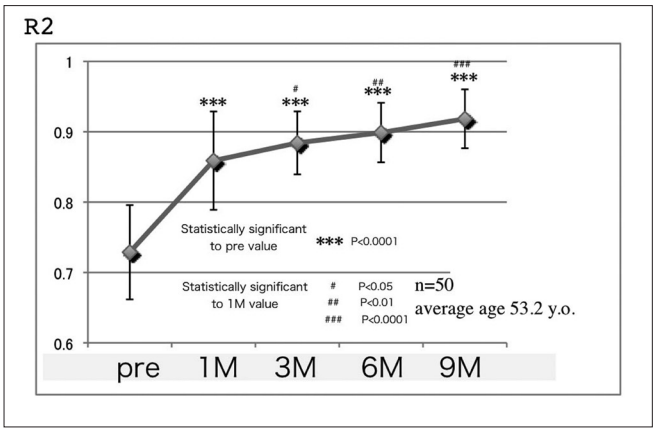

Figure 5: Variation in R2 values over time after a single dose of bFGF (n=50)

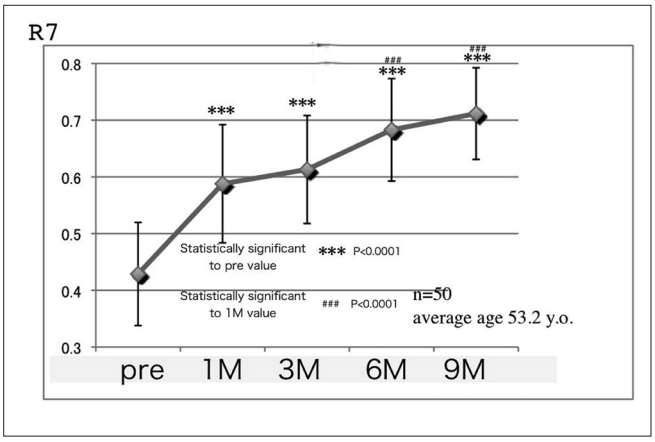

Figure 6: Alterations in the R7 value over time after a single dose of bFGF (n=50)

Clinical course of representative cases

Following is the summary of the clinical courses of several cases representative of the subjects who received the one-time treatment with the test solution. This manuscript presents longer term results of clinical follow-up, in addition to the results of the viscoelasticity measurements performed up to 9 months. The improvements lasted for longer than 9 months in almost all of the patients, and for longer than 2 years in some patients.

Case 1

A single dose of the test solution was infused to the dorsal surface of the right hand of a 44-year-old female. Nine months after the treatment, the skin turgor had increased markedly and protuberant venous veins were alleviated, indicating apparent rejuvenating effects. The favourable changes progressed up to the 12 post-treatment month and were retained thereafter. The detailed follow-up observation showed improvement for up to 21 months without any additional treatment [Figure 7a-h].

Case 2

A single dose of the test solution was infused to the dorsal surface of the right hand of a 50-year-old female. The rejuvenating effects were apparent for up to 9 months after the treatment and remained up to the 31st post-treatment month without any additional treatment [Figure 8a-c].

Case 3

A single dose of the test solution was infused to the dorsal surface of the right hand of a 54-year-old female. Observation at 9 months after treatment revealed a marked increase of skin turgor and increased skin thickness, alleviation of protuberant veins and tendon, and marked alleviation of the recessed region between the extensor tendons and remained up to the 24th post-treatment month without any additional treatment [Figure 9a-c].

Case 4

A single dose of the test solution was infused to the dorsal surface of the left hand of a 66-year-old female. Observation at 9 months after treatment revealed a marked increase of skin turgor with increased skin thickness and considerable alleviation of the protuberant veins and tendon, indicating remarkable rejuvenating effects. The effects have been retained to the present, or for 28 months post-treatment, without any additional treatment. This case proves that rejuvenating effects can be expected even among elderly subjects [Figure 10a-c].

DISCUSSION

While complete UV blocking is thought to prevent photo-aging, no method has yet been developed to rejuvenate skin once it has aged.[1-4] Meanwhile, the dramatic increases in average life expectancy in recent years place great demands on QOL in later life. From a cosmetic standpoint, a rejuvenating method with safe, reliable, and long-lasting effects is eagerly awaited.[4] The mainstay treatments for skin rejuvenation nowadays are cosmetic surgeries, epidermal resurfacing, skin tightening (lasers, high radio-frequency (RF), intense pulsed light,[9] etc.), and autologous fat injection. There are also popular treatments with temporal effects, such as filler injections and wrinkle-removal via neuroparalysis induced by neuroparalytic agents.[5-10] The injection of a platelet-suspended solution (PRP)[15,16] has also gained attention, but the procedure is complicated and the effects vary from patient to patient and are undependable for the elderly. Broadly speaking, none of these treatments are fundamental or physiological, and none of them confer long-lasting or permanent effects.[17] Skin aging remains as a problem to be solved.[18-20]

A number of recent papers have drawn attention by reporting rejuvenating effects of growth factors applied

Figure 7: Case 1: A 44-year-old female treated on the dorsal surface of the right hand. (a) Pre-treatment. (b) Post-treatment 1 month. (c) Post-treatment 3 months. (d) Post-treatment 5 months. (e) Post-treatment 9 months. (f) Post-treatment 12 months. (g) Post-treatment 16 months. (h) Post-treatment 21 months

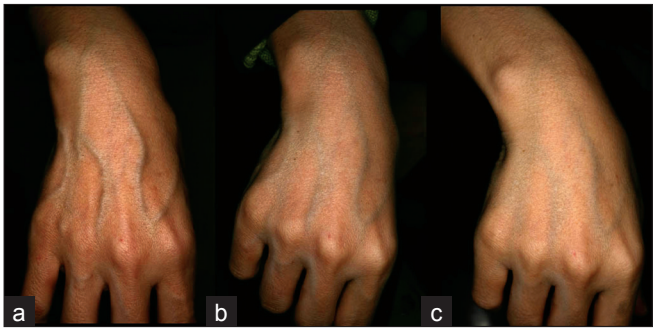

Figure 9: Case 3: A 54-year-old female treated on the dorsal surface of the right hand. (a) Pre-treatment. (b) Post-treatment 9 months. (c) Post-treatment 24 months

topically.[21-24] Yet we know from the molecular weights of growth factors that percutaneous absorption cannot be expected. In the method we developed for this study, the first method of its kind in the world, the growth factor is injected directly into the dermis of the affected skin. The treatment agent thus administered induces inflammation in the dermis at the affected site and thereby confers rejuvenating effects. Our growth factor is superior to conventional drugs for injection such as fillers and the botulinium toxin, as it exerts fundamental effects that are both safe and long lasting.

As we have already reported,[12-14] the test solution containing growth factor has superior effects on the dorsal surface of the hand. The present clinical trial is the first to use growth factor for rejuvenation, however, to use a long-pulse Alexandrite laser for the removal of pigmented macules. We applied this laser treatment in one third of our subjects and found that it had very little influence on the rejuvenation effect we report. The

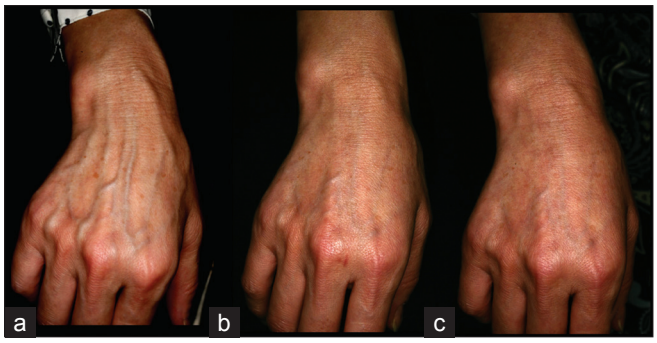

Figure 8: Case 2: A 50-year-old female treated on the dorsal surface of the right hand. (a) Pre-treatment. (b) Post-treatment 9 months. (c) Post-treatment 31 months

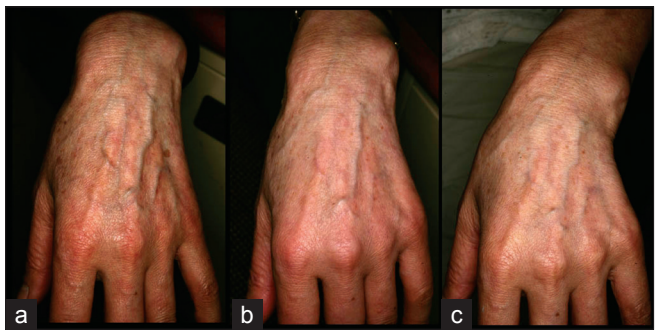

Figure 10: Case 4: A 66-year-old female treated on the dorsal surface of the left hand. (a) Pre-treatment. (b) Post-treatment 9 months. (c) Post-treatment 28 months

treatment of the senile pigmented macules by the long-pulse Alexandrite laser treatment was limited to sites with pigmented macules, and the rejuvenating effects induced by the growth factor in the laser-treated subjects were comparable to those in the subjects who received no laser treatment. We expect our growth factor treatment has potential for use as a rejuvenation therapy for the neck, trunk and extremities, as well as the face.

The duration of the effects we report, 2 or more years, is certainly epoch making, but we still need to investigate the duration of the effects more precisely in longer term follow-up observations. This doctor-directed clinical study spanning 3 years and 6 months confirmed that the treatment effects progressed gradually for the first 9 months to 1 year after the treatment, and that with a complete blockage of UV rays, the condition could be retained for 2 or more years. We assume that the excellent effects observed were attributable to factors beyond the oral vitamin C and UV block alone. As such, we speculate that the rejuvenating effects obtained in this study stemmed mainly from the intradermal administration of the growth factor.

Cutometer measurements from earlier studies have already demonstrated that skin viscoelasticity which indicates the biomechanical properties of the skin in normal age-groups decreases with age.[25-29] Similarly, the

viscoelasticity of the dorsal surfaces of the hand decreased with age in all of the age-groups investigated in the current study. The R2 value was 90% or higher in subjects in their 20s and 30s and decreased linearly in subjects in their 40s onwards, and the value measured in subjects in their 60s or above was about half of the value measured in the young. Meanwhile, the R7 value decreased progressively from decade to decade starting from before the 30s, and the value measured in subjects in their 50s was about half of the value measured in the young. This clarified that skin viscoelasticity decreases with age and that R7, a value believed to reflect the immediate elasticity (post-0.1-second return rate), starts to decrease earlier than R2, a value indicated by the post-2-second return rate. Various factors expressed as solar elastosis, such as the drying and thinning of the skin and the degeneration and reduction of elastic and collagen fibres, are thought to be closely involved in this mechanism. In the observations of the dorsal surface of the hand, the R2 value changed from a level corresponding to an age of 61.2 years before treatment to a level corresponding to an age of 34.7 at 9 months after treatment. The R7 value changed from a level corresponding to an age of 57.8 years before treatment to a level corresponding to an age of 33.3 at 9 months after treatment. Thus, the changes in the R2 and R7 values, that is, the alterations in viscoelasticity which indicates the biomechanical properties of the treated aged skin, from pre-treatment to post-treatment, corresponded to age differences of more than 20 years (26 years and 24.5 years, respectively).

Many points remain to be solved before the mechanism behind the rejuvenating effects of the intradermal administration of growth factor is fully known. Various phenomena are involved in the treatment, including the induction of inflammation, subsequent cellular growth, neogenesis of elastic and collagen fibres, induction of fibroblast cell death, and the early disappearance of myofibroblasts.[30-33] Moreover, the neogenesis of elastic and collagen fibres at the treated site may play a very important role. Subsequent studies have revealed that bFGF helps to reduce scarring when applied to suture wounds and confers similar treatment effects when applied to scars or keloids. There is strong evidence to suggest that apoptosis is involved in these effects.[34-38]

Although we have observed no serious harmful side effects, careful follow-ups will be required to determine the risk of inducing malignant tumours by the intracutaneous infusion of single doses of growth factor. We believe this treatment to be extremely safe in this regard. The test agent has been used clinically as a spray agent for the treatment of ulcers in Japan since 2001 without any major harmful events. Further, we encountered no critical harmful events involving carcinogenesis in our previous study on intradermal administration to suture wounds as a treatment to prevent scarring[34]. Another major problem in this treatment with growth factor is the pain caused by the intradermal infusion. This problem can be solved by sufficient local anesthesia before treatment, but the commercialization of products for local administration with less pain, the implementation of clinical studies, and legal approvals are all eagerly awaited.

None of our subjects manifested induration in the treated dorsal surfaces, but several of them did manifest facial induration at the early stage of our study. Because this phenomenon has not occurred since the administrations were limited carefully to dermis or sites just under the affected skin, it was inferred that the phenomenon occurring in the beginning was likely the result of an injection to the subcutaneous fat tissue or muscle layer as did with fillers. We were able to prevent this phenomenon by carefully localizing the injection to the dermis or to the sites just under the affected skin.

There have been no other reports on the rejuvenating effects of growth factor infused intradermally. This makes us the first group in the world ever to attempt this treatment approach. This test agent has been commercialized as a spray agent for treating ulcers, but only in three countries, that is, Japan, Korea, and China. Thus, direct infusion to the skin for the purpose stated in this study will require approval under the Helsinki Declaration and laws and regulations of concerned countries. The approval of ethic committees will also be essential. To this end, physicians sufficiently experienced and skilled in this field should confirm the safety of the test agent, create a uniform treatment method, and carefully conduct self-directed clinical studies. We also believe that it will be essential to conduct multi-centre joint studies to accurately evaluate the safety and effects of this treatment method and detect harmful events at an early stage.

Future progress and wide clinical application will require new adjective studies and strict attention to legal compliance to assure the safety of the subjects. Over time, we expect our growth factor treatment to be greatly accelerated by combinations of multiple growth factors in protein form or with peptides, or in gene form or with stem cells.[38-41] Ultimately we hope to establish a new paradigm for creating an effective treatment strategy for growth factor rejuvenation.

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