

Advances in the research of autologous fibroblast injections for aging skin

Meng-Yao Tang, Rong Jin, Ying Zhang, Yao-Ming Shi, Bao-Shan Sun, Lu Zhang, Yu-Guang Zhang

Department of Plastic and Reconstructive, Shanghai Ninth People's Hospital affiliated to Medical School of Shanghai Jiao Tong University, Shanghai 200011, China.

Address for correspondence: Prof. Yu-Guang Zhang, Department of Plastic and Reconstructive, Shanghai Ninth People's Hospital affiliated to Medical School of Shanghai Jiao Tong University, No. 639 Zhi Zao Ju Road, Shanghai 200011, China. E-mail: zhangyg18@126.com

ABSTRACT

With the development of autologous stem cells transplantation, the application of autologous fibroblast graft has been an important therapy in defect repair. In the past decade, amounts of studies have reported favorable treatment effect and safety about the therapy. The material has the ability to produce human collagen *in vivo*. This article details recent scientific work of the cases, effect, injection technique, complications and safety of autologous fibroblast injection treatment.

Key words:

Autologous fibroblast; injection; aging skin

INTRODUCTION

Wrinkles can be corrected by using various treatment methods like lasers, soft tissue fillers, Botox for dynamic wrinkles, and so on. The most common therapy is dermal fillers like hyaluronic acid. However, dermal fillers are typically degradable or semipermanent, and liable to allergic reaction or other side reactions like skin necrosis, visual impairment.^[1] Autologous materials have been used for more than a century for soft tissue augmentation. Autologous fat has always been the first choice of autologous graft. However, the high rate of graft resorption and unpredictable degree of volume loss in some degree reduced the enthusiasm for the use of adipose grafts in soft tissue augmentation.^[2] With the development of autologous stem cells transplantation, the application of autologous fibroblast graft has been an important therapy in defect repair.^[3-7] Fibroblasts are the main functional cells in dermis and autologous fibroblasts injection may be more beneficial than other therapies in facial rejuvenation.^[8] Autologous fibroblasts injection is not

a common kind of dermal filler, that is to say, it is not volume filler. As a result, it's very important to notify patients that the therapy does not take effect in a short time. Fibroblasts show mitigating improvement after about 3 serial treatment processes and living cells keep vigorous growth that may lead to greater persistence than other fillers.^[9] Autologous cultured fibroblasts have been used effectively for dermal and subcutaneous deficiencies since 1995.^[10] Autologous fibroblast transplantation first received approval from the US Food and Drug Administration in June 2011 to improve moderate or severe nasolabial fold wrinkles.

CASES AND TREATMENT OUTCOME

In the past decade, amounts of studies have reported favorable treatment effect and safety about the therapy.^[11-13] Clinical researches for autologous fibroblast therapy have been carried on since 2001. Cultured autologous fibroblasts

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: service@oaepublish.com

How to cite this article: Tang MY, Jin R, Zhang Y, Shi YM, Sun BS, Zhang L, Zhang YG. Advances in the research of autologous fibroblast injections for aging skin. *Plast Aesthet Res* 2016;3:83-5.

Received: 02-11-2015; **Accepted:** 10-12-2015

Access this article online

Quick Response Code:



Website:
http://parjournal.net

DOI:
10.20517/2347-9264.2015.118

have been utilized effectively to treat various wrinkles, depressed scars, acne irregularities,^[14] wounds^[15] and atrophy.^[16,17]

In 2007, Weiss *et al.*^[18] in America reported a double-blind, randomized comparison on autologous fibroblast injection and placebo for facial contour defects treatment. Results showed that autologous fibroblasts generated statistically significantly greater improvements in dermal deformities and acne scars than did placebo. The difference between fibroblast injections and placebo obtained statistical significance at 6 months ($P < 0.0001$). Patients treated with autologous fibroblasts continuously show benefit at 9-month and 12-month follow-up. There were no serious treatment-related adverse events in this study.

In 2012, Smith *et al.*^[19] reported a multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy to treat nasolabial fold wrinkles. A large sample including 372 subjects was enrolled in this trial. There were comparisons between subjects treated with cultured autologous fibroblast and placebo. The results showed at least 1-point improvement on both subject and evaluator assessment after 6 months ($P < 0.001$).

In 2012, in a South American study, Eça *et al.*^[20] published the results of their search about the safety and efficacy of dermal regeneration with the injection of young autologous fibroblasts obtained from patients themselves. With 4 injections given at 15-day intervals after 60 days, periorbital tonicity had improved obviously. Nevertheless, there was little improvement in surface lines and no improvement at all in deeper wrinkles.

In 2013, Munavalli *et al.*^[12] in America reported a randomized multicenter, prospective, double-blind, placebo-controlled clinical trial about the treatment of bilateral moderate to severe acne scars using autologous fibroblasts. Ninety-nine subjects underwent three intradermal injection sessions at 14-day intervals. They were injected autologous fibroblast suspension on one cheek and cell culture medium on the other cheek. The outcome showed that autologous fibroblast had significantly greater efficacy than vehicle control (cell culture medium).

INJECTION TECHNIQUE

Different anesthesia forms are provided at the discretion of the investigator. A topical anesthetic cream containing 4% lidocaine may be applied. The areas of treatment are swabbed with an antiseptic before injections.

Autologous fibroblast suspension or placebo is injected using a 1-mL syringe and a 29- or 30-G needle. A retrograde linear threading technique is utilized. The suspension is placed into the superficial papillary dermis. Create a wheal and transient blanching of the skin surface with each injection. The current injection dose is 0.1 mL of suspension with a concentration of $(1.0-2.0) \times 10^7$ cells/mL. During the

injection, doctors should pay attention to the following points:

- No lidocaine or epinephrine is mixed to the cell suspension before injection to avoid the negative impact on the viability of the cells.
- No massage or other manipulation of the areas is performed to avoid damaging or altering the cells.
- No soaps, cosmetics, or any other products are used to the injection sites for 72 h after operation. Limited short-term indirect application of ice to the treatment area was allowed but not recommended.^[19]

Injections can be given in the forehead wrinkles, perioral wrinkles, nasolabial fold, chin, and periorbital wrinkles with a minimal interval of 15 days between each session. The injection technique has no obvious difference among these different injected sites.

COMPLICATIONS AND SAFETY

There is no record in the scientific literature of any case of tumor formation resulting from the stem cell injection since the first transplants of adult stem cells from bone marrow in the 1960s^[21] and the transplant of adult stem cells from umbilical cord blood in 1988.^[22]

Autologous fibroblast therapy has been considered to be safe and well tolerated in amounts of researches. The wrinkle improvement during this treatment is different from most dermal fillers. The product results in the accumulation of new collagen but not direct volume replacement. Consequently, it has a more gradual onset of effect than which has been seen immediate correction from other dermal fillers.^[19]

Autologous fibroblast therapy has adverse events including: local redness, bruising, swelling, bleeding, pain or irritation, erythema, developing nodules, nausea, headache and so on. The most common adverse events reported were redness, swelling, and bruising in and around the treatment areas. The severity of majority of adverse events is mild to moderate and probably related to the process of injection.

CONCLUSION

Autologous fibroblast treatment is a novel therapeutic method for treating dermal defects. The material has the ability to produce human collagen *in vivo*. In sum, autologous fibroblasts injection has the following characteristics: (1) it's not a volume filler; (2) injection level is more superficial; (3) need a period of time (about 6 months) to take effect; (4) treatment effect on fine lines like nasolabial wrinkles is better; (5) need additional costs and processes for harvesting and culturing fibroblasts before injection; and (6) adverse reactions are minimal and comparable with other common injection. Although the favorable outcomes have been obtained from various studies, the specific cellular and molecular biologic mechanism remains unknown. They may take effect through single or several signal pathways that could

cause direct synthesis of increased amounts of collagen and elastin, proliferation of fibroblasts and the deposition of cofactors.^[23] This may be the long-term goal of the autologous fibroblast transplantation research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg* 2014;134:1197-201.
- Illouz YG. Present results of fat injection. *Aesthetic Plast Surg* 1988;12:175-81.
- You HJ, Han SK, Rhie JW. Randomised controlled clinical trial for autologous fibroblast-hyaluronic acid complex in treating diabetic foot ulcers. *J Wound Care* 2014;23:521-2, 524, 526-30.
- Milinkovic I, Aleksic Z, Jankovic S, Popovic O, Bajic M, Cakic S, Lekovic V. Clinical application of autologous fibroblast cell culture in gingival recession treatment. *J Periodontol Res* 2015;50:363-70.
- Morimoto N, Ito T, Takemoto S, Katakami M, Kanda N, Tada H, Tanaka S, Teramukai S, Kawai K, Nakamura Y, Kasai Y, Masayuki Y, Maekawa T, Shimizu A, Suzuki S. An exploratory clinical study on the safety and efficacy of an autologous fibroblast-seeded artificial skin cultured with animal product-free medium in patients with diabetic foot ulcers. *Int Wound J* 2014;11:183-9.
- Pichler R, Klima G, Richter E, Marksteiner R, Mayr V, Skradski V, Horninger W, Oswald J. Autologous fibroblast transplantation at the vesico-ureteral junction as potential reconstructive cell replacement in an animal model. *World J Urol* 2013;31:169-74.
- Malecki M. Improved targeting and enhanced retention of the human, autologous, fibroblast-derived, induced, pluripotent stem cells to the sarcomeres of the infarcted myocardium with the aid of the bioengineered, heterospecific, tetravalent antibodies. *J Stem Cell Res Ther* 2013;3:pii 138.
- Martin I, Baldomero H, Bocelli-Tyndall C, Slaper-Cortenbach I, Passweg J, Tyndall A. The survey on cellular and engineered tissue therapies in Europe in 2009. *Tissue Eng Part A* 2011;17:2221-30.
- Weiss RA. Autologous cell therapy: will it replace dermal fillers? *Facial Plast Surg Clin North Am* 2013;21:299-304.
- Boss WK Jr, Usal H, Fodor PB, Chernoff G. Autologous cultured fibroblasts: a protein repair system. *Ann Plast Surg* 2000;44:536-42.
- Shevtsov MA, Galibin OV, Yuditceva NM, Blinova MI, Pinaev GP, Ivanova AA, Savchenko ON, Suslov DN, Potokin IL, Pitkin E, Raykhtsaum G, Pitkin MR. Two-stage implantation of the skin- and bone-integrated pylon seeded with autologous fibroblasts induced into osteoblast differentiation for direct skeletal attachment of limb prostheses. *J Biomed Mater Res A* 2014;102:3033-48.
- Munavalli GS, Smith S, Maslowski JM, Weiss RA. Successful treatment of depressed, distensible acne scars using autologous fibroblasts: a multi-site, prospective, double blind, placebo-controlled clinical trial. *Dermatol Surg* 2013;39:1226-36.
- Jin Z, Wu YG, Yuan YM, Peng J, Gong YQ, Li GY, Song WD, Cui WS, He XY, Xin ZC. Tissue engineering penoplasty with biodegradable scaffold Maxpol-T cografted autologous fibroblasts for small penis syndrome. *J Androl* 2011;32:491-5.
- Munavalli GS, Smith S, Maslowski JM, Weiss RA. Successful treatment of depressed, distensible acne scars using autologous fibroblasts: a multi-site, prospective, double blind, placebo-controlled clinical trial. *Dermatol Surg* 2013;39:1226-36.
- Morimoto N, Kakudo N, Valentin Notodihardjo P, Suzuki S, Kusumoto K. Comparison of neovascularization in dermal substitutes seeded with autologous fibroblasts or impregnated with bFGF applied to diabetic foot ulcers using laser Doppler imaging. *J Artif Organs* 2014;17:352-7.
- Zhao Y, Wang J, Yan X, Li D, Xu J. Preliminary survival studies on autologous cultured skin fibroblasts transplantation by injection. *Cell Transplant* 2008;17:775-83.
- Milinkovic I, Aleksic Z, Jankovic S, Popovic O, Bajic M, Cakic S, Lekovic V. Clinical application of autologous fibroblast cell culture in gingival recession treatment. *J Periodontol Res* 2015;50:363-70.
- Weiss RA, Weiss MA, Beasley KL, Munavalli G. Autologous cultured fibroblast injection for facial contour deformities: a prospective, placebo-controlled, phase III clinical trial. *Dermatol Surg* 2007;33:263-8.
- Smith SR, Munavalli G, Weiss R, Maslowski JM, Hennegan KP, Novak JM. A multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy for the treatment of nasolabial fold wrinkles. *Dermatol Surg* 2012;38:1234-43.
- Eça LP, Pinto DG, de Pinho AM, Mazzetti MP, Odo ME. Autologous fibroblast culture in the repair of aging skin. *Dermatol Surg* 2012;38:180-4.
- Thomas ED, Lochte HL Jr, Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest* 1959;38:1709-16.
- Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A, Esperou H, Thierry D, Socie G, Lehn P. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989;321:1174-8.
- Lamme EN, Van Leeuwen RT, Brandsma K, Van Marle J, Middelkoop E. Higher numbers of autologous fibroblasts in an artificial dermal substitute improve tissue regeneration and modulate scar tissue formation. *J Pathol* 2000;190:595-603.