Commentary

Commentary on: Topical Nanofat Biocrème Improves Aesthetic Outcomes of Nonablative Fractionated Laser Treatment: A Preliminary Report

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Diane I. Duncan, MD, FACS

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The author is to be congratulated on addressing an emerging practice for skin regeneration employing topically applied nanofat plus a compounded liposomal delivery vehicle.[1] Though topical application of nanofat or allogeneic stem cells is relatively common, literature resources on the subject are surprisingly sparse.[2-5] Nanofat harvest and processing systems are readily available (Lipocube, Tulip) among others. The practice of enriching standard adipose grafts with nanofat is thought to enhance graft take.[6]

Many practitioners have begun employing some form of progenitor cells in their practices, as the phrase "stem cell" seems to promise miraculous outcomes to the consumer. Although intra-articular injections of platelet rich plasma are popular, the results can be unpredictable. In our community, the charge for injection of either autologous or allogeneic Mesenchymal stem cells is roughly 10 times that of a simple platelet rich plasma injection.

The practice of utilizing nonthermal and thermal-based microneedling to enhance both biological and dermaceutical uptake has become well known and widely practiced during the last several years.[7] Although dermaroller or nonthermal microneedling is popular and widely used, the literature supports the utilization of thermal microneedling or laser-assisted drug delivery for enhanced topical delivery of an active agent.[8]

Despite the FDA warning letter issued[9] noting that any application of a topical agent intended to change the structure or function of a human below the stratum corneum could be seen as a drug subject to FDA approval, the missive noted abstinence from current enforcement. Recently,[10] the federal agency released a warning against topical application of allogeneic umbilical cord-derived cells due to the risk of infection. Although the tissue processing rules for banked umbilical cord tissue are rigorous,[11] the FDA does not regulate their topical use at this time.

When the art and science of fat transfer began to be practiced, particle size was not as important as viability. Though Gause notes that larger grafts seem to have greater overall viability, no regenerative effects were noted in his publication.[12] Recently, classification of fat graft types has gained attention because each is employed for a different purpose.[13] Macrofat, with a particle diameter of greater than 2.4 mm, contains some stroma and is utilized for a more defined contour. This type of graft would be avoided in regions with thin skin, such as the infraorbital region. Millifat, with a particle size of 2.4 cm or less, has less chance of creating visible lumpiness post grafting. Microfat, defined as a 1- to 1.2-mm-diameter fat particulate, can be injected in the deep dermis with a 23- to 25-gauge needle. Nanofat is injectable using a 27-gauge or smaller needle or cannula (Figure 1).

Dr Duncan is a plastic surgeon in private practice in Fort Collins, CO.

Corresponding Author:
Dr Diane Irvine Duncan, 1701 East Prospect Road, Fort Collins, CO 80525, USA.
E-mail: momsurg@aol.com; Twitter: @DrDuncanPSA

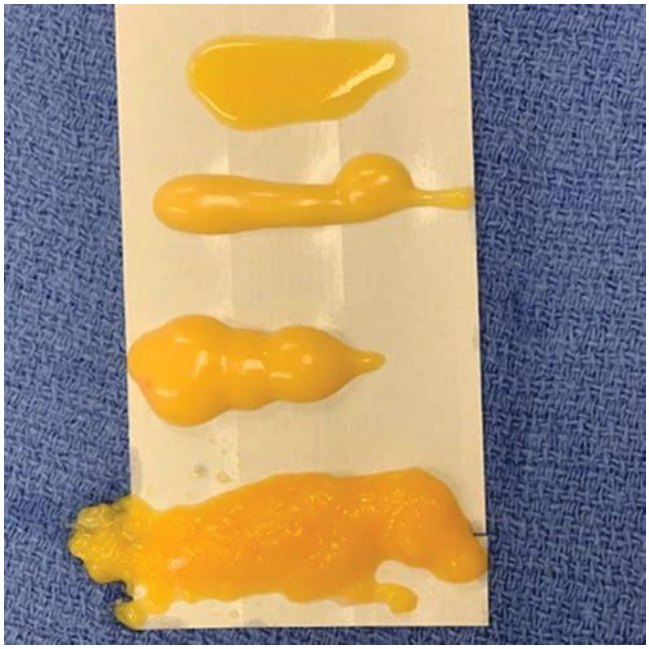

Figure 1. Types of fat for grafting. From top to bottom: nanofat, microfat, millifat, and macrofat.

Figure 2. Cost-effective device for superficial injection of nanofat.

There are no adipose cells in nanofat.[14] The particle size of the tissue following processing utilizing a microprocessor such as Nanocube (Lipocube, London, UK) is about 490 microns. However, even these small particles are poorly absorbed into nonthermal microchannels due to their early plugging with fibrin clots.[15] Another reason that topically applied nanofat may not be effectively absorbed is their inherent fragility. Once the cells become dry, viability is significantly impaired. Therefore, the concept of adding both hydration and a liposomal delivery system has great merit. Even with this combination of cells plus a vesicular delivery system following thermal "needling" (in this case laser-assisted drug delivery), we do not know how many progenitor cells remain viable. Because topical nanofat application is relatively new, data on long term viability as well as the mechanism of action are scarce.

Objective evaluation of clinical efficacy is needed to ensure both safety and efficacy for future patients. Employing 3 measurement systems—independent evaluation utilizing an unbiased observer and a relative improvement scale, as well as a controlled histological evaluation of skin treated with laser alone and laser plus the topical biological, adds credence to the idea that transdermal application of the enhanced mixture actually works.

The authors were honest in admitting the limitations of the study. Another bit of additional information that would be helpful to the reader would be the steps in mixing processed nanofat into the biocrème, as well as the source of the compounded delivery crème, so that interested practitioners could perform the procedure. The degree of long-term improvement in wrinkles, texture, elasticity, and tone remains unclear. It would be interesting to test topical application of nanofat without the additional agent vs application with the biocreme, as many practitioners do not protect the cells from desiccation.

Other delivery systems might include hydrogels,[16] nanosheets,[17] self-assembling proteins,[18] or exosomes.[19,20] The recent emergence of exosomes as a proposed drug delivery system for nanofat is probably fallacious, because particle size of most exosomes is tiny, less than 100 microns. Lipophilic systems, similar to the one used in this study, may have an advantage over hydrophilic vesicles given the cell wall's structure as a lipid bilayer.[21] The addition of a chemical agent such as phosphatidylcholine[22] may improve diffusion characteristics, though phosphatidylchine alone is difficult to reconstitute. When considering topical drug delivery, one must consider the targeted cell destination, access beneath the stratum corneum, the diffusion characteristics of the biologically active agent, and the mechanism of transport. In the case of live cells, the biggest challenge might be to keep them viable.

In the future, we may find that superficial intradermal injection of nanofat has both clinical and biological advantages over topical application. Multiple needle mesotherapy devices (Hydra Needle, MesoGold 20, etc.) come in a variety of programmed depths (0.6. 1.0, and 1.5 mm). These single-use devices have multiple needles and can deliver cells into the dermis with accuracy and speed (Figure 2). Although nanofat can be injected with a 27-gauge needle, accurate spacing of the intradermal spots can be challenging

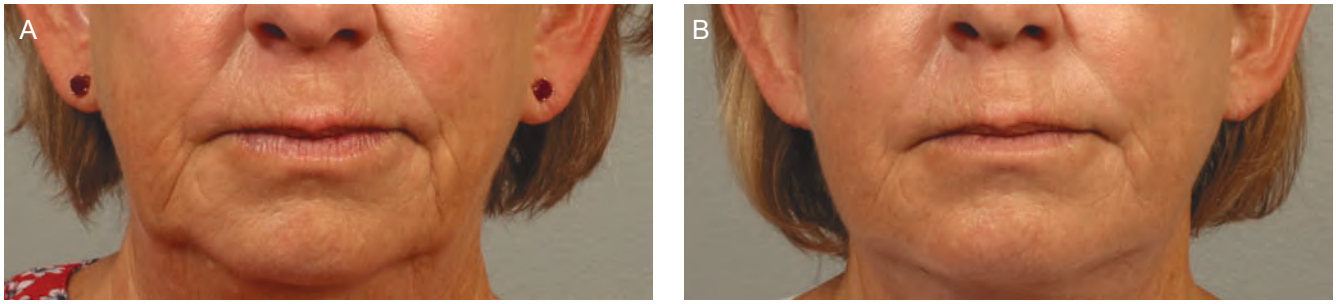

Figure 3. (A) This 68-year-old woman prior to treatment. (B) Six weeks post-nanofat injections to facial skin, perioral lines, and wrinkles. No other treatment was performed.

when using a single needle. The injection of linear defects with nanofat can be effective in treating fine to moderate wrinkles, especially in the perioral region or necklace lines (Figure 3). Although microfat and nanofat have not been reliably proven as fillers, the concept of utilizing autologous cells instead of artificial fillers is attractive to many patients.

A final safety concern is that of utilizing allogeneic tissue as anything other than a topical agent. Reports of serious infections employing umbilical cord blood-derived products have been noted by the FDA.[23] Although intravenous injection of stem cells derived from banked tissue is permitted in the Cayman Islands and Bahamas, long-term health concerns have not been addressed. The capability of migration of these cells to systemic sites populated with tumorigenic cytokines and cell markers has been noted.[24] Although systemic embryonic tissue injection is not permitted in the United States, unsuspecting medical tourists may be at risk in seeking these treatments elsewhere.

The field of utilization of Mesenchymal stem cells and human derived adipose stem cells is rapidly evolving. Due to the significant potential commercial gain from employing stem cell terminology, both patients and practitioners are at risk when requesting and providing these services. Long-term risks and benefits are not well known. At this point, ultimate safety is paramount. Therefore, the utilization of autologous rather than allogeneic cells is recommended for any purpose other than topical use.

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