MESOTHERAPY: TECHNIQUE NOT TREATMENT

Pam Cushing INP explores the history and growth in the use of mesotherapy techniques to deliver treatments in aesthetic practice

As our society is growing older, the consequences of ageing, particularly skin ageing, has gained special attention. Evidence has broadened our understanding of the factors that influence ageing - skin cell function, cell-to-cell interaction, and intermolecular transport and communication. This has stimulated an interest in the application of mesotherapy, a technique involving micro-injections into the papillary dermis using active and essential ingredients directly stimulating fibroblast cells. Clinical experience supports the technique as a simple, safe, cost-effective and acceptable treatment modality performed by suitably trained practitioners who follow safe injection practice with appropriate aseptic techniques.

The skin

As the largest organ, the skin is sophisticated, dynamic and serves as a bastion between the delicate internal organs and the external environment. It is viewed not only as a barrier. It maintains internal hydration, sensory perception, and immunological surveillance and is an excellent thermo-regulator (Farage et al., 2013). Its appearance reflects overall general health and communicates ethnicity, lifestyle, financial status, and age. As life expectancy in industrialised countries increases exponentially, there is an increasing demand by consumers to maintain a youthful appearance. This demand is driving the growth of new dermatological procedures for the treatment of skin ageing. Inherent in the focus of reversing the visible signs of ageing is the need to address the loss of structure and function of the skin and how these manifest in the quality of life.

The skin-like all systems of the body eventually succumb to the unrelenting effects of ageing. As a complex biological process, ageing skin is influenced by a combination of intrinsic and extrinsic processes (Gancevicience et al., 2012). These processes lead to cumulative structural and physiological alterations in each skin layer as well as the skin's appearance.

Intrinsic ageing occurs at a genetically pre-determined pace caused primarily by the buildup of reactive oxygen species (ROS), a by-product of cellular metabolism which damages cellular components, membranes, enzymes and deoxyribonucleic acid (DNA) (Farage et al., 2013). With advancing age, skin loses its structural and morphological characteristics, and its functions deteriorate. Makrantonaki et al. (2012) argue intrinsic ageing is multifactorial and is influenced by gene expression in response to extrinsic assault as well as genes displaying defects in replication, repair and transcription. They also correlate a link to down-regulation of lipids, a decline in hormones, and changes differing widely among ethnic populations and between genders.

Fisher et al. (2008) postulate that collagen deficit from alteration in the extracellular matrix (ECM) rather than intrinsic or UV irradiation damage to fibroblasts is primarily responsible for the visible signs of ageing. Quan et al. (2013) and Sparavigna et al. (2015) concur, suggesting the reduction in the ECM is highly responsible for the wrinkling and sagging of the skin.

However, they all hypothesise that regulating fibroblast function to maintain optimum levels of collagen production throughout the individual's lifetime would improve the health and appearance of the skin. This suggests that interventions to delay skin ageing by adopting strategies to prevent, regenerate and delay ageing

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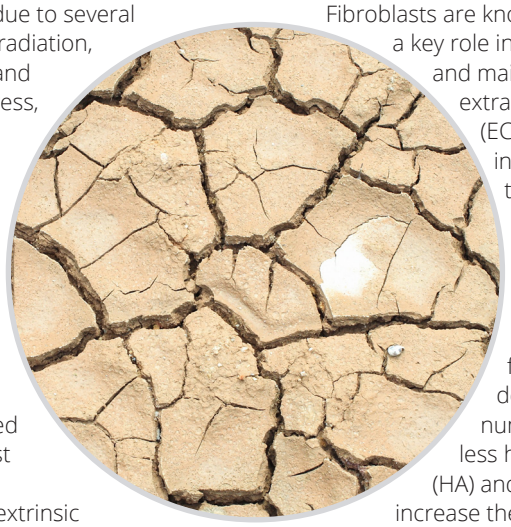
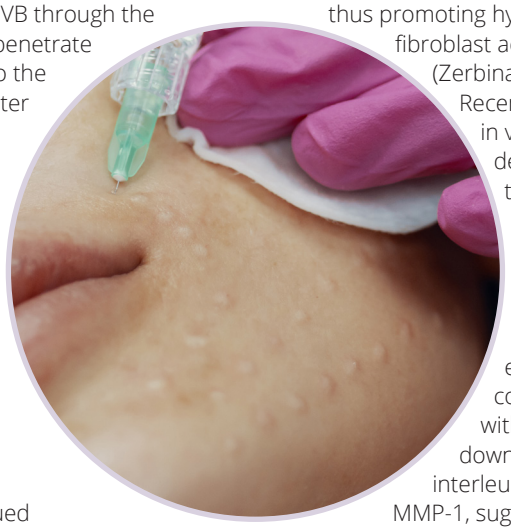
will continue to influence research in aesthetic medicine.

However, extrinsic skin damage and ageing develop due to several factors: ionizing radiation, severe physical and psychological stress, alcohol intake, poor nutrition, overeating, environmental pollution, and UV radiation (UVR). Chronic UV exposure resulting in DNA damage and UV-generated ROS is the largest causative factor associated with extrinsic photo-ageing. Amaro-Ortiz et al. (2015) postulate that UV radiation produces direct and indirect DNA damage, with 80% of the visible signs of ageing attributed to UV exposure. The extent of damage that occurs is directly proportional to the amount of sun exposure and inversely proportional to the genetically predetermined amount of skin pigmentation.



Fair-skinned individuals produce less eumelanin, a dark brown pigment highly effective at absorbing UV photons, so they are much more prone to the acute and chronic effects of UV radiation. It has been convincingly demonstrated that UVB (290-320 nm), UVA (320-400 nm), and Infrared (IR) A (770-1400 nm) can induce extrinsic skin ageing. UVA penetrates through the epidermis; UVB through the dermis and IRA penetrate all three layers to the subcutis (Vierkotter and Krutmann, 2012). This results in the formation of photoproducts that inactivate the function of DNA as well as damage to mitochondrial DNA (mtDNA), leading to visible signs of ageing skin. The continued mitochondrial damage is positively associated with an increase in matrix metalloproteinase-1 (MMP) without concomitant MMP-1 Inhibitors reducing collagen 1 expression (Fisher et al., 2008, Vierkotter and Krutmann, 2012, Poljsak and Dahmane, 2012, Quan et al., 2013).



Fibroblasts are known to play a key role in producing and maintaining the extracellular matrix (ECM), so crucial in maintaining the integrity of the skin's appearance. Through the natural ageing process, fibroblasts decrease in number, produce less hyaluronic acid (HA) and collagen, and increase the production of enzymes responsible for collagen degradation. There is also a loss of mechanical interactions with the surrounding ECM. Prikhenko (2015) suggests that whilst the exact mechanisms are unclear, increases in oxidative stress and an imbalance between production and elimination of ROS is an important contributor to ageing. Fibroblasts, however, retain the capacity for functional activation, making them viable targets for anti-ageing treatments.

Several experimental studies have demonstrated that Hyaluronic acid (HA) injected into the skin stimulate the fibroblasts to express collagen type 1, matrix metalloproteinase-1 (MMP-1), and tissue inhibitor of matrix metalloproteinase-1 (TIMP), thus promoting hydration and fibroblast activation (Zerbinati et al. 2021). Recent clinical and in vitro studies demonstrated that a formulation rich in HA, vitamins and amino acids increased the expression of collagen type 1 with concomitant downregulation of interleukin IL-1 IL-6 and MMP-1, suggesting a link with the inflammatory processes (Deglesne et al. 2016).

Advances in the understanding of biochemical mechanisms associated with ageing have led to the development of different approaches to reduce and repair using minimally invasive procedures. In recent years, there has been an increasing emphasis on Mesotherapy as one of the many tools and techniques in our armamentarium to impede the intrinsic and extrinsic ageing process.

What is mesotherapy?

Mesotherapy is a method of drug delivery using multiple and micro-dosed injections of bioactive products and compounds into the skin. The aim is to stimulate cellular activity and reconstruct an optimal physiological environment for the fibroblasts to increase the synthesis of collagen, elastin, and HA.

The mechanism of action is the skin acts as a natural time-release system with the solutions injected remaining in the area longer due to slower vascular clearance. The more superficial the injection, the longer the solution remains in the area (Lather and Vandana 2011).

Studies on the intradermal administration of medication for anti-inflammatory, anaesthetic and antibiotics have demonstrated the slow systemic absorption - local spread allows for a lower dose of the drug, and a lower frequency of administration, as compared to the systemic route (Mammucari et al., 2011).

As a technique, however, mesotherapy is not a modern phenomenon. The use of needles for alleviating symptoms has been used since ancient times, with Hippocrates (400BC) using cactus spines and ointment mixed from the barbaric fig leaf for the treatment of shoulder pain. Acupuncture with and without ointment is a practice unchanged for over 2,000 years. The invention of the hollow needle by Gabriel Pravas in 1832 heralded the development over the last century in the local and systemic injection of various drugs to alleviate pain and symptoms of disease (Le Coz 2005). In 1867, Gaetano Primavera carried out the first experiment to assess the degree of drug absorption in the urine after hypodermic injection. The results supported the hypothesis that low dose produced measurable clinical effects better than deep injection. In 1941, George D. Gammon and Isaac

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Starr published the analgesic effect of sterile water inoculated over or in the proximity of the pain (Mammucari et al., 2020).

The term 'Mesotherapy', first coined by Dr Michel Pistor in his first publication in 1958, followed years of treating patients with local injections to alleviate a variety of ailments. He defined the term as a treatment of the mesoderm, *meso* being 'middle', referring to the effects of the local injection directly in the target region.

The overarching principle of Mesotherapy is defined as "*little-infrequently-in-the-right-place*". Pistor founded the French Society of Mesotherapy in 1964 with the technique extending to treat general medical, veterinary and cosmetic conditions.

The French National Academy of Medicine officially acknowledged it as a medical specialty in 1987, and mesotherapy has continued to gain popularity across Europe, South America and the United States of America (Le Coz 2005, Sivagnanam 2010).

However, in 2004, Sergio Maggiori analysing pre-clinical and clinical trials, proposed the term 'local intradermal therapy' (LIT) as a more accurate representation of the superficial application, and the emphasis on the clinical effect with a lower dose of active ingredients (Mammucari et al., 2020).

The acceptance by stakeholders internationally is multifactorial; inexpensive equipment, relatively minimal training, reduced drug dose required with minimal untoward effects, quick results, minimally invasive, relatively pain-free and inexpensive.

Hyaluronic Acid (HA)

The most frequently used substance used for facial rejuvenation or bio-revitalisation is natural, non-crossed linked HA. HA is well known to accumulate and retain 1,000 times its body weight in water and provides enrichment of one of the main ECM compounds, deeply hydrating the skin and stimulating fibroblasts to produce collagen type 1 and MMP-1 inhibitors (Savoia et al., 2013, Sparavigna et al., 2015). The injection process also produces a small inflammatory response that triggers a repair mechanism in the skin leading to collagenesis (Madhere 2007).

Various studies have demonstrated improvement, not only in skin integrity and appearance, but also a degree of photo-protection with complexes containing HA, as well as vitamins, amino acids, antioxidants, and nucleotides. Vitamins have core functions as antioxidants and in collagen synthesis and cellular metabolism. Amino acids are required to build ECM proteins. Minerals regulate cell homeostasis, and nucleosides replicate DNA and ribonucleic acid (RNA) for protein synthesis (Baspeyras et al., 2013, El-Domyati et al., 2013, Savoia et al., 2013, Prikhnenko 2015, Sparavigna et al., 2015). These studies conclusively demonstrated clinical and biophysical changes confirmed by instrumental evaluations.

However, a couple of studies report disappointing findings (Amin et al., 2006, El -Domyati et al., 2012). It could be argued the formulations used in these studies and treatment protocol may influence the overall outcomes. A review of the protocol adopted for these studies leads the author to suggest the time frame between each treatment was too protracted to facilitate the cumulative effects of the formulations used.

Each injection in the studies was pre-mixed with HA and multi-vitamins before the subject injection. Prikhnenko (2015) states that putting multiple components together is not enough to guarantee their efficacy.

Latha and Vandana (2011) remind us that the FDA has not approved mesotherapy, despite the technique being widely used and supported by eminent dermatologists. They argue that compounding drugs to meet the unique needs of the patient produces a 'new drug' that would require approval.

The author suggests that practitioners, when deciding on which formulation to introduce into practice, need to consider this before choosing their patient-specific formulations over pre-formulated complexes. The author also warns a review of the wording on the packaging will guide them regarding the appropriate application of the chosen formulation.

In the marketplace, there is an abundance of mesotherapy products supporting bio-revitalisation and the important role it has to play in skin rejuvenation available from various manufacturers. Selection and the composition of these formulations may prove daunting to the practitioner, but an understanding of the physiological effects of the individual components can help to demystify these complex therapies (see table). There may be slight variations in the composition depending on the treatment area and degree of rejuvenation required between manufacturers, but most will have the same primary class of ingredients, so it's inherent that a detailed examination of all products is undertaken before selection.

Class	Component
Vitamins and vitamin-like sub-stances	Vitamin A (Retinol), Vitamin C (Ascorbic acid), Vitamin E (tocopherol), Inositol, Vitamin B1, B2, B3, B5, B6, B8, B9 B10, B12.
Minerals	Calcium chloride, Potassium chloride, Magnesium sulphate, Sodium acetate, Sodium chloride, Sodium dihydrogen phosphase
Amino acids	Alanine, Arginine, Asparagine, Aspartic acid, Cystine, Glutamine, Glutamic acid, Glycin, Histidine, Hydroxyproline, Isoleucine, Isoleucine, Leucine, Lysine, Methionine, Ornithine, Phenylalanine, Proline, Serine, Taurine, Threonine, Trypophan, Tyrosine, Valine
Nucleosides	Deoxyadenosine, Deoxycytine, Deoxyguanosine, Deoxythymides, Methylcytosine
Co-enzymes	TPP, CoA, FAD, NAD, NADP, UTP
Other anti-oxidants	Glutathione
Hyaluronic acid	Non-reticulated sodium hydrouronate

Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) has gained considerable attention in the field of dermatology since the elucidation of the mechanism and clinical effects. PRP can induce remodelling of the ECM, increasing the expression of MMPs to remove photodamaged ECM components and stimulate the proliferation of dermal fibroblast and collagen synthesis. PRP has gained popularity in the management of not only skin concerns and disorders, such as vitiligo and melasma but, also the management of some forms of alopecia. Several studies have demonstrated the efficacy of using PRP and mesotherapy in the treatment of fine lines and wrinkles.

Lin et al. (2020) identified in their study that PRP mediated skin rejuvenation is not dose-dependent, citing that 5% PRP more strongly induced procollagen type 1 than 10% PRP. In vitro studies support the findings with higher fibroblast proliferation with 5% vs 10% PRP. A study conducted by Abuaf et al. (2016) identified the number and thickness of the collagen fibre bundles and elastin fibres were significantly increased with PRP. The authors of this study concluded the increase was not only through the growth factors but also the action of skin needling using the mesotherapy technique.

Botulinum Toxin A (BoNT-A)

The use of Botulinum Toxin A (BoNT-A) is well established in aesthetics with a strong efficacy and safety profile. The potential application of its use in off-label indications has seen an increase in the use of BoNT-A as intradermal injections, particularly in the management of the symptoms of rosacea.

As a skin disorder, rosacea is a complex and complicated inflammatory disease whose aetiology is linked to two distinct pathogenic mechanisms. The first being the presence of abnormal neurovascular signals, which activate the release of vasoactive peptides. These are usually triggered by different factors - heat, spicy food, or alcohol (Luque A et al., 2021).

The second mechanism is a dysregulation of the innate immune system, with abnormally high levels of cathelicidin LL-37. This increase in LL-37 forms active peptides Kallikrein 5 (KLK5) which cleave a cationic antimicrobial protein 18 (CAP18) to form active peptides in the epidermis. The subsequent increase in KLK5 causes an increase in cathelicidin LL-37 leading to inflammation, typical in rosacea-prone skin. Various studies identified mast cells as key enablers of the increase in cathelicidin LL-37-induced skin inflammation. All identified a significant reduction in cathelicidin LL-37, mast cell degranulation, and mRNA expression of rosacea markers following intradermal injection of BoNT-A (Choi et al., 2019, Zhang H, Tang, Wang Y, Fang R and Sun Q, 2021).

Mesotherapy injection techniques

The injection techniques used in Mesotherapy differ from other techniques, so require training and practice to develop dexterity and precision. The injections can be done manually or with the use of an automated device or 'Mesogun'. The manual technique requires practice to avoid unnecessary pain and bleeding, with the common techniques used being intra-epidermal, papule, or nappage. The needles adopted are 30 gauge (4mm or 13mm) and should be used bevel up.

- **Intra-epidermal**: 1mm depth. Simple to perform, allowing coverage of a large area, non-painful, no bleeding, acts rapidly, causes cutaneous stimulation.
- **Papule**: 1mm-2mm. Raised bleb formed at the junction of the epidermis and dermis. Used to treat facial rhytides. Greater accuracy when using specific mesotherapy needles of 4mm
- **Nappage**: 2mm-4mm. Most commonly used technique in Europe. Injections every 2-4mm, at an angle of 30-60° with constant pressure on the plunger with a wrist flicking action. Able to cover large areas, significant cutaneous stimulation, more discomfort, rapid action.

The mesogun, however, enables injections to be delivered in a standard and reproducible way, avoids wastage of the chosen complex, and is virtually pain-free if set at rapid repetitions. The author finds this device an indispensable tool facilitating a high degree of patient safety and accuracy of depth and dose for each injection point and is well tolerated by patients.

The emergence of small, micro-channelling devices into the aesthetic market, e.g., WOW Fusion and Aquagold Fine Touch, have become a more cost-effective alternative to a mesogun. These devices provide the same benefits as a mesogun - a set needle length, a reduction in the wastage of active ingredients and solutions and, depending on the needle depth, they are virtually pain-free.

The devices are particularly useful in treating the symptoms of rosacea using BoNT-A as all studies used multiple intradermal injections using the papule technique, which is painful even when administered by skilled practitioners.

Patient selection

As with all aesthetic procedures, patient consultation is vital for improved patient/practitioner relationship and shared decision-making. A visual assessment of the face, including skin type, is necessary to elucidate the eventual outcome as well as limitations of the treatment.

Whenever possible accurate photography of the skin is a simple objective method of recording. This acts as a 'benchmark' and a record of the appearance, texture, colour, pigmentation, and sallowness and supports the continued assessment as to the effectiveness of the treatment regime.

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A full medical history in addition to known allergies, intolerances, medication and food supplements, predisposition to pigmentation and keloid scarring are critical to identifying the potential for adverse outcomes. Oral anticoagulants are not necessarily a contraindication, but treatments should be limited to the superficial layers to avoid bruising and bleeding. Absolute contraindications include,

- Pregnancy
- Known hypersensitivity to known ingredients
- Insulin-dependent diabetes mellitus (IDDM)
- Liver and kidney disorders
- AIDS/HIV
- Skin cancer
- Active acne
- Unrealistic expectations

A review of their general lifestyle activities will allow the practitioner to educate the patient on changes in behaviour and lifestyle that will enhance the overall results.

In certain cases, the need for combination therapy such as botulinum toxin A (BoT-NA), dermal fillers, chemical peels or microdermabrasion will achieve a better overall result. Patients need to be reminded that mesotherapy is not a 'quick fix', and the need for repeated treatments at regular intervals will be necessary to achieve the desired effect.

The aim is to improve the overall integrity and appearance of the skin, so the patient looks and feels better rather than 'looking younger'. It is crucial to understand the patient's wishes and expectations to deflect the potential for dissatisfaction and 'complaint'.

Complications

The side effects and adverse outcomes following mesotherapy are rare in experienced hands. Appropriate training and ongoing education are vital to retaining competence and skill.

The most common side effects are invariably procedure-related such as pain, erythema, oedema, bruising, bleeding, itching, and discrete scratch marks. Hypersensitivity to HA will present immediately, or within 15minutes, with a raised pruritic rash (Chase 2005).

Faulty and poor attention to aseptic techniques leads to localised infections and erythematous nodules. Several cases of cutaneous *Mycobacterium abscessus* infection have been reported following mesotherapy and soft tissue augmentation procedures by unlicensed practitioners, and in cases with poor attention to aseptic techniques plus inappropriate cleaning with contaminated tap water (Sivagnanam 2010, Wongkitisophon et al., 2011, Prikhnenko 2015).

The frequency of treatments is largely dependent on patient compliance, fiscal status, and pre-treatment skin assessment.

As a general rule, 3-6 treatments, depending on baseline status at 2-week intervals, is recommended with a maintenance treatment every six months.

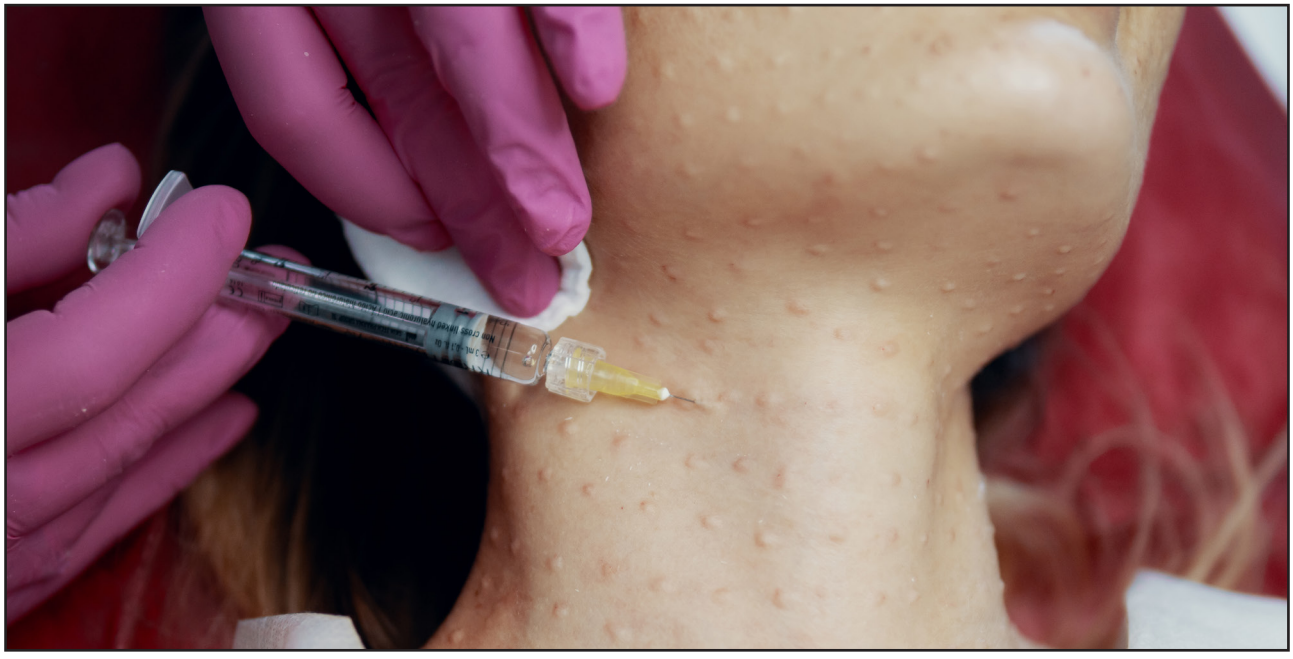
Concomitant gentle skin peeling is an excellent preparation before treatment as this improves the active substance uptake. BoNT-A, along with dermal fillers, may be performed in the same appointment without any deleterious effects.

Conclusion

Mesotherapy has been widely and successfully used as a treatment for skin ageing. The increasing concern to maintain a youthful appearance is driving the growth of new procedures, with the emphasis on minimally invasive, safe and effective procedures. Intradermal injections of biological formulations have demonstrated the ability to induce revitalisation and stimulate qualitative and quantitative improvements in skin ageing. The goal is to create a favourable microenvironment for optimal fibroblast biosynthesis activity.

Clinical studies, alongside international experience, support the effectiveness of mesotherapy while studies on safety and efficacy hover through uncertain territory.

However, we need to bear in mind, "*Just as the absence of proof is not proof of absence, lack of scientific validation is not proof it does not work*".



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