

Mesodermal Minuscule Depot of Drug Delivery Protocol: A Review

Zeba Siddiqui¹, Ashutosh Shukla², Rahul Srivastava³

¹Intern, ²Senior Lecturer, Department of Oral and Maxillofacial Surgery, ³Reader (Oral Department of Medicine and Radiology, Rama Dental College Hospital and Research Centre, Lakhanpur Kanpur, India

Corresponding author: Dr Zeba Siddiqui, Plot no 52, 116/630 Bageecha Basheer, Krishnapuri, Rawatpur, Kanpur, Uttar Pradesh, India (208019).

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A B S T R A C T

Mesotherapy is a medical specialty that involves the introduction of various therapeutic agents like natural extracts, homeopathic agents, pharmaceuticals and vitamins in microscopic quantity to the skin. Mesotherapy has various therapeutic applications. Factors that provide wider reception of mesotherapy includes affordable armantarium, comparatively less training for the providers, limited dose of drugs with resultant minimum chances of untoward effects, minimally invasive/painful outpatient procedure with early positive results.

This article highlights the possible mechanism of action, indications, contraindications and therapeutic applications of mesotherapy.

Key words: Mesodermal Minuscule, Drug

INTRODUCTION

This medical technique was introduced in 1952 by renowned French physician, Dr. Michel Pistor for the management of pain and vascular disorders.^{1, 2}

The name mesotherapy was introduced by Michel Pistor for the first time in an article published on June 4th 1958, emphasizing on the advance properties about effect of local procaine in human pathology. "The effect on the tissues of the mesodermis is so significant that these treatments deserve the global name of mesotherapy."³

He further elaborated it as treatment of the mesoderm (the primary germ layer which develops into connective tissue, muscles and circulatory system) referring to the effectiveness of local procaine on these wide number of tissues.⁴

In 1961 his first book, *La Mésothérapie (Mesotherapy)* is published. Further in 1968 he presents a dissertation before the Academy of Medicine in May. The title is: *Mesotherapy, a Versatile Technique*.³

In 1976 the first hospital outpatient service for mesotherapy was created. In the same year, the first International Mesotherapy Congress takes place in Bray-Lu.³

In 1987, mesotherapy was officially acknowledged as a medical specialty by The French National Academy of Medicine. After the death of Pistor in 2003 it will be a fitting tribute to worldwide pronounce Dr Pistor as the 'Father of Mesotherapy'.⁵

In this technique multiple intradermal or subcutaneous

injections are introduced in small doses, using fine gauge needles to cure medical (specifically local) and cosmetic conditions. These injections are mixture of compounds like plant extracts, homeopathic agents, vitamins, and other bioactive substances. The term 'meso' which also means 'middle' and 'mean', hence variably explained in reference to the route of administration of the drug i.e. into the middle layer of skin or 'intradermotherapy'.⁶

Mesotherapy is a non-invasive non surgical cosmetic medical treatment which utilizes series of injections to perfuse liquid preparation inclusive of traditional pharmaceutical and homeopathic medications, vitamins, mineral, amino acids, plant extracts and other ingredients into the subcutaneous tissue ('mesoderm') to cure local medical and aesthetic conditions.⁷ These injections apparently targets the adipose fat cells, by inducing lipolysis and cell death among adipocytes.⁸ The local medical and aesthetic conditions can easily treated with help of mesotherapy that utilizes a series of medicated injections.⁷

Mesotherapy is promoted as a 'non-surgical alternative to liposuction' as the most significant indication are reduction of adipose tissue including cellulite, lipomas and weight loss.⁹⁻¹¹

Mesotherapy is based on the principle of Local Intradermal Therapy (LIT) where a 'micro deposit' of the drug in the dermis which then is slowly released into the surrounding tissues. LIT allows effective concentration of

the drug to reach the target area though it only permits lower doses to be administered compared with p.o./i.m. routes. His method does not alter the mechanism of action of a given drug, which remains unchanged irrespective of the administration site. A drug administered intradermally remains in the surrounding tissue for longer than the same drug administered i.m.

LIT reduced the total drug dosage needed to treat a given low-regional condition.¹²

To achieve results in Mesotherapy one must need:

1. Professional training.
2. Proficient Protocols.
3. Precise Techniques.
4. Effective Equipment and Supplies.
5. Superior Quality Ingredients.¹³

REQUIREMENT OF MESOTHERAPY

1. Ingredients: In mesotherapy all ingredients must be water soluble, isotonic, and non-allergic and do not cause nodules, abscess or necrosis at injection site.

2. Syringes: Most commonly used syringes in this therapy are 5cc to 20 cc slip tip syringes and 5cc to 20cc luer lock syringes.

3. Needles: "Lebel needle" are most commonly used in mesotherapy.

Recommended needles for application:

Face and neck- 4mm 30G Mesotherapy Needles.

Cellulite and fat- 6mm 30G Mesotherapy Needles and ½ inch 30G Needles.

4. Multi injectors and plates: Circular Multi Injectors- 7 NEEDLES- suitable for all body parts. Linear Multi Injectors- 5 NEEDLES- suitable for all body parts. Mesotherapy Gun- suitable for all body parts and allows different injection techniques.

5. Automatic injection device: An ample number of models and types of automatic mechanical, electronic guns are available to facilitate the practice of Mesotherapy. The practitioners of this technique affirms the benefits of these injection devices in rendering minimally painful experience to the patient, comfortable for the practitioner, as well as adding precision and consistency to injections. Some significant benefit of Mesotherapy guns include:

1. Increased comfort level for the patient and complacency for the practitioner.
2. Minimally painful experience due to skin stabilizer, speed of needle and consistency of injections.
3. Maximum operator dexterity without fatigue.
4. Accuracy- the procedure is programmable and consistent with no room for operator error.
5. Versatility- Precisely performs continuous, nappage, mesoperfusion and dosimetric modes.
6. Speed- Procedures are fast with quick results.¹³

MODE OF ACTION

A general mode of action for mesotherapy has been proposed.

The mode of action for mesotherapy has been proposed.

"The dermis is a common denominator of three units i.e. circulatory, neuro-vegetative and immunological functions. It has been proposed that by the action at each of these units, mesotherapy corrects the functional disorder that causes the suspected pathology".¹⁴

Mesotherapy utilizes both chemical and physical (mechanical) stimulation of the circulatory unit, immune competence unit, nervous competence unit and fundamental competence unit within the dermis and subcutaneous tissue, which promotes the lymphatic, immune and circulatory system of the body to create a biological response and reverse abnormal physiology.

The solutions injected intradermally remain in the injected area for a longer duration compared to subcutaneous ones, and act as a natural time-releasing agent up to 7 days, the injected drug target the adjacent problematic area and continue to diffuse into the deeper tissues at the same time.

This technique is also used to stimulate the mesoderm for various other biological purposes. For instance, In case of poor circulation, a vasodilator is used; if excessive inflammation/stimulation is needed, a fibroblast proliferating solution is injected. Conditions such as lymph veno lymphatic insufficiency in case of cellulite a stimulator of venous and lymph flow is used.¹⁵

TECHNIQUES OF INJECTION

The choice of injection technique (either manual or mesotherapy gun) is important as it determines the quality of the results obtained. The results will vary considerably according to the technique depending on the injection site, the pathology treated, the structure of the dermis and the products injected.

1. ME (Mesotherapy epidermique)
 - Retarded effect, bleeding (-), pain (-) 30 G, 13 mm needle
2. Papule (intra basal injection)
 - Superficial intradermal technique.
 - Injecting the product at the junction of epidermis and dermis, peeling epidermis at the basal lamina.
 - Needle at a depth of 1-2 mm, with the bevel facing upwards.
 - Appearance of a pale, clearly delineated papule at the time of injection signifies an accurate technique.
 - The papule fades within the space of few minutes and disappears entirely within next 30 minutes.
3. Nappage (multi-pricking injection)
 - Discovered by Dalloz Bourguignon.
 - Most commonly used technique.

- It shows semi-retarded effect.
 - Series of injection 2-4mm apart, regular and constant pressure on plunger.
 - A 4mm needle inserted at 30-60 degree angulation at a depth of 0.5-2mm is used.
 - 2-4 injections/sec are delivered in this technique.
 - Variation in this technique with an epidermal nappage, applying the product to the epidermis at a depth of less than 1mm.
 - Advantage- minimum bleeding.
4. PPP (Point-by-point)
 - Deep intradermal or hypodermic injection technique.
 - 4 or 6 mm needle is used.
 - Delivered 0.03~0.1 ml/point, at 0.5~ 2 cm distances.
 - This technique is punctual and painful, more or less profound.
 - Indicated in rheumatology, sports pathology and aesthetic medicine for the treatment of cellulite. Particularly suited to targeting deep nodules or for fibro- sclerous cellulite.
 5. Mesoperfusion
 - Also known as sequential mesotherapy (MS) or Mesotherapy lente.
 - Needle at 2-13mm depth, 5-45 minute (1-5 second injection 10-50 second intervals sequentially)
 - Effective in chronic pain
 6. MPS (Mesotherapie Pontuelle Systematisee)
 - Dermo-hypodermic injection (2-10 mm) into injected at fixed objective, and reproducible points.
 - Mesotherapie seche et mouillee
 - Mixed
 7. Classification by injection depth
 - IED (intra-epidermic injection): <1mm
Technique: ME, superficial nappage
 - IDS (superficial intra-dermic injection): 1~2mm
Technique: papule, IDS nappage
 - IDP (profound intra-dermic injection): 2~4mm
 8. Technique: PPP, mesoperfusion
 - IHD (intra-hypodermic injection): 4~10mm
Technique: PPP, mesoperfusion, MPS
 - DHD (dermo-hypodermic injection): used in MPS.^{13,15}

Hasegawa T reported a case of a 42-year-old man suffering from benign symmetric lipomatosis with multiple, large, symmetrical masses present in his neck. Multiple phosphatidylcholine injections were administered in the neck 4 weeks apart and it took a total of seven times to achieve lipolysis and he found that phosphatidylcholine mesotherapy can be use as therapeutic option for this disease.¹⁶

Görgülü T evaluated the efficacy of hair mesotherapy technique for the treatment of eyebrow problems. Twelve patients with complain of weak and sparse eyebrows were

treated with eyebrow mesotherapy. On an average 67% (8 out of 12 patients) were satisfied with the results on the 15th day of the procedure and clinically thickening and darkening of colour could be be appreciated.

He concluded that eyebrow mesotherapy is a minimal invasive and comparitvely less painful method that may be opted prior to invasive and irreversible methods, such as eyebrow transplantation and tattooing.¹⁷

Savoia A evaluated the efficacy of mesotherapy technique for facial rejuvenation. The two formulations were used: Formulation A which consists of hyaluronic acid, amino acids, minerals, vitamins, coenzymes and antioxidants substances; and formulation B with hyaluronic acid and idebenone.

This study enrolled 50 participants who were divided in two groups, Group 1(50-65 years) treated with formulation A. Group 2 (35-50 years) treated with formulation B. The group underwent four sessions of mesotherapy involving multiple injections.¹⁸

ADVERSE EFFECTS OF MESOTHERAPY

The side effects caused due to mesotherapy are mostly minor and reversible like:

- 1. General Effects** – Burning or itching sensation, Tenderness, pain, swelling or bruising.
 - 2. Potential Side Effects** – Flushing, vagal response, allergy, dizziness, nausea.
 - 3. Local Effects** – Hematoma, necrosis, abscess, hyper pigmentation, infections (mycobacterium).
- Mostly the adverse effects occurs due to:

1. Medication
 - Generalized/localized redness of skin.
 - Epigatralgia
 - Lipothymia
 - Cephalous.
2. Technique and/or route of administration
 - Infection
 - Pain
 - Manifestations of cutaneous or sub-cutaneous conditions
3. Perforation technique
 - Hematoma
 - Tattoos
 - Achromic Scar
 - Necrosis
 - Burn
 - Mechanical lesions.¹³

MINIMIZING SIDE EFFECTS

Allergic Reactions: Procaine is the agent mainly responsible for any allergic reaction during the treatment, though no clear cases of allergic shock have however been

reported in the course of mesotherapy.

The most common reaction described is mainly rashes which disappear in 2-3 days. However immediate termination of the treatment should be done in case of any noticeable allergic reaction.

Pain: The pain experienced by the patient depends on uncontrollable factors like sensitivity of the area treated, patient sensitivity, and depth of the injection.

The two factors to be considered for pain reduction are:

1. Technique of injection: Injection must be quick and precise.
2. Armamentarium: Both the mesotherapy gun and needles should be of good quality and the needles must be regularly changed during the sessions covering large areas.

Infections: Skin acts like a protective barrier between the body and infections. By keeping in mind certain precautions they can be avoided:

1. Best quality products offering all the necessary guarantees of sterility
2. Proper sterile and disposable equipments.
3. Following proper surgical site disinfection guidelines.
4. Proper hygiene maintenance of the area treated.

Hematoma: Hematoma is the most common side effect observed in patient undergoing mesotherapy. Ordinarily, hematomas tend to undergo resorption within 2-3 days and leave no long term sequelae. Unfortunately this process can take quite some time and the general appearance can be quite unpleasant in the interim, in that case it can be easily masked with makeup. Avoiding inadvertent nicking of vessels and capillaries during the procedure will assist in reducing the instance of hematoma.¹³

INDICATIONS OF MESOTHERAPY

Dr. Le Coz has stated 120 conditions in which mesotherapy have proved to be effective including the following:

- Cellulite Reduction.
- Obesity.
- Stretch marks.
- Carpal Tunnel Syndrome.
- Alopecia.
- Face: Acne, scars, Enlarged pores and greasy skin, Wrinkles of face and neck, Double chin, Dark circles, slackened and swollen circles under eyes, Slackening of the facial contours.
- Muscle Relaxation.
- Flaccid or couperose skin.
- Skin pigmentation or splotchy complexion.
- Refreshing and smoothening of hands.
- Migraines.
- Tendonitis.
- Sports trauma.

- Recovery from plastic surgery.
- Bone spurs.
- Dissention.
- Arthritis pain.
- Hyper- pigmentation.
- Hyperkeratosis.
- Chronic Infections.^{13,19}

CONTRAINDICATIONS

Mesotherapy should be avoided in case of:

- Diabetic patients.
- Oncological disorders.
- Cholelithiasis.
- Allergy.
- Acne.
- Epilepsy
- Active herpes
- Use of antithrombotic medicine.
- Infection or inflammation in the treated site.
- Cardiovascular diseases.
- Pregnant or breastfeeding women.^{19,20}

MEDICATION IN MESOTHERAPY

The drug of choice injected during Mesotherapy depends upon the pathophysiology of the disease and may include:

- Local Anesthetics.
- Vasodilators.
- Phlebotonic agents.
- Immunostimulants.
- Metabolic regulators.
- Trace elements.
- Muscle relaxants.
- Corticoids.
- Vasoactive drugs.
- Hormones.
- Antibiotics.
- Phytotherapeutic agents.
- Anti-inflammatories.
- Antispasmodics.
- Analgesics.
- Neurotrophic agents.
- Sedatives.
- Homeopathic medicines.
- Biologicals.
- Antihomotoxic preparations.
- Decontractants.
- Proteolytic enzymes.
- Vaccines.¹³

AMERICAN SOCIETY FOR PLASTIC SURGEONS (ASPA) GUIDING PRINCIPLES OF MESOTHERAPY

1. It is the responsibility of individual's physician to

Local anesthetic	Lidocaine, Marcaine, Xylocaine, Procaine.
Dilutents	Saline, NaCl.
Disinfectants	70% alcohol, Betadine, Biseptine.
Anti-inflammatory	Calcitonin, Ketoprofen, Piroxicam.
Lipolytic	Aminophylline, Artichoke Extract, Caffeine, L-Carnitine, Triac.
Nutritional	Multivitamins, Pantothenic Acid, Zinc, Copper, Biotin, Vitamin C.
Cosmetic	Hyaluronic Acid, Conjonctyl Mellilottus.
Metabolic stimulants	Glycolic Acid, Retinoic Acid
Enzymes	Hyaluronodase, Collagenase.
Fat dissolve	Deoxycholate and/or Phosphatidylcholine.
Circulation	Trental, Beta Blockers, Pentoxifylline, Propanolol.
Hormones	Estrogen, Progesterone.
Hormones blockers	Finasteride, Dutasteride.
Neurological	Valium, Amitriptyline, Bentlyl.

understand and abide by all applicable Federal, State and local regulations.

- Only those drugs which are FDA approved should be commercially advertised; it is illegal to commercially advertise any non-approved or off-label use.
- An appropriate informed consent should be ensured by the physician for each patient prior to the treatment. The consent should clearly state that there is very limited scientific evidence available to verify the efficacy of mesotherapy and/or injection lipolysis for the treatment of dissolving fat accumulations.
- Because safety and efficacy cannot be ascertained from the available body of English literature, ASPS believes further scientific testing of fat reduction mixtures is needed before recommendations on their use may be formally issued.
- Physicians administering mesotherapy treatments should be aware of the chemicals/drugs being injected, dosages, particular side effects, and potential interactions.
- Records of injected substances and dosages administered should be available in the patient's medical record and accessible to other treating physicians.
- Physicians should use their personal and professional judgment while interpreting and applying these guiding principles to their individual practice. These guiding principles should not be considered as rules or standards of medical care.²¹

CONCLUSION

The upper layers of skin has protective barrier against environmental exposure and reduce the absorption of topical therapeutic agents. Mesotherapy gets through this barrier and provide direct access for nutrients and various

pharmacological agents into the mesoderm, the deepest layer of skin. Mesotherapy covers a broad spectrum of injuries, disorders and medical conditions, along with treating cosmetic conditions. Due to its non-invasive, painless nature mesotherapy gained popularity. However continued research and scientific studies are required to substantiate the claims of effectiveness of this technique.

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Local drug delivery depots have significant clinical utility, but there is currently no noninvasive technique to refill these systems once their payload is exhausted. Inspired by the ability of nanotherapeutics to target specific tissues, we hypothesized that blood-borne drug payloads could be modified to home to and refill hydrogel drug delivery systems. To address this possibility, hydrogels were modified with oligodeoxynucleotides (ODNs) that provide a target for drug payloads in the form of free alginate strands carrying complementary ODNs. A drug-loaded tumor cell (DLTC) system has been developed for lung metastasis-targeting drug delivery. Doxorubicin was loaded into B16-F10 murine melanoma cells (96 microg/10(6) cells). In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 1b, remaining constant, between the desired maximum and minimum, for an extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to 1 month (Lupron Depot) to 5 years (Norplant). Figure 1. Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing. In recent years, controlled drug delivery formulations and the polymers used in these systems have become Drug delivery system can use passive targeting which utilizes the enhanced permeability retention effect (EPR). EPR is present in tumor tissues. Preparation of liposomes and their usage as drug delivery vehicles. So far numerous different procedures for preparation of liposomes have been developed like sonication, extrusion, freeze-thawing, microemulsification and membrane extrusion. These methods can be divided in two groups, a "top-down" and "bottom-up" approach.