



Microneedling: A Primer for Dermatologists

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Abstract

Microneedling is a minimally invasive procedure that is becoming widely utilized in dermatology. Microneedles (MNs) are fine, needle-like structures that penetrate the skin. MNs can be used for percutaneous collagen induction (PCI) therapy and to augment transdermal drug delivery. This review is a primer on microneedling for dermatologists. It provides an overview of the history, instruments, principle of PCI, drug delivery mechanism, applications for dermatologic conditions, and adverse effects. For MN applications in dermatology, PubMed database was used to search for studies and search terms included “microneedling” and “percutaneous collagen induction.” Priority was given to studies with human subjects and prospective, randomized trials. Studies demonstrate success with microneedling for skin rejuvenation, acne scars, non-acne scars, acne vulgaris, hyperpigmentation, alopecia, hyperhidrosis, and drug delivery. The procedure is reported to be safe with minimal adverse side effects. As MN use becomes more widespread, it is important to increase the number of randomized, controlled trials to provide further data on the efficacy and safety of microneedling.

Introduction

Microneedling is a minimally invasive procedure that is becoming widely utilized in dermatology. Microneedles (MNs) are fine, needle-like structures that penetrate the skin. In percutaneous collagen induction (PCI) therapy, MNs penetrate the dermis and lead to the reorganization of collagen fibers and release of growth factors that stimulate the formation of new collagen, elastin, and capillaries in the skin [1]. Microneedling can also augment transdermal drug delivery through creation of micropores. It has been explored for a wide variety of dermatologic conditions.

This review is a primer on microneedling for dermatologists. It provides an overview of the history, instruments, principle of PCI, drug delivery mechanism, applications for dermatologic conditions, and adverse effects. PubMed database was used to search for studies and search terms included “microneedling” and “percutaneous collagen induction.” Priority was given to studies with human subjects and prospective, randomized trials.

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History

The term “microneedle” was first described in 1976. This new technology was originally developed with the intention to overcome the limitations of conventional transdermal drug delivery [2]. With advances in manufacturing and contemporary micro fabrication techniques in the 1990s, a great variety of MNs were created. In 1995, Orentreich and Orentreich described “subcision” (“subcutaneous incisionless” surgery) or dermal needling for treatment of scars [3]. They inserted a tri-beveled hypodermic needle through a puncture in the skin surface and its sharp edges were maneuvered under the defect to make subcuticular cuts or “-cisions.” This case series found success in treating depressed scars and wrinkles, with a proposed mechanism of creating controlled trauma to promote new connective tissue formation under the defect and long-term collagen remodeling. In 1997, Camirand and Doucet described needle dermabrasion using a “tattoo pistol” to treat scars [4]. Based on these principles, in 2006, Fernandes developed the derma roller for “percutaneous collagen induction therapy” [5].

Instruments

There are two main types of microneedling instruments: derma rollers and pens. Derma rollers are hand-held devices with MNs projecting from a cylindrical roller on one end. The roller is applied directly to skin and rolled across the desired area. One example is the Derma roller CIT-8, a medical device approved for professional use only. It has 24 circular arrays of eight needles located on the roller. There are 192 needles in total and the needles are 200 µm in length with a 70 µm diameter. There are many other variations of the derma roller available for both medical and cosmetic use and

for use by professionals or at home. Major issues with derma rollers are poor regulation of home derma rollers and unsubstantiated claims. Other disadvantages are that they are single use; disposable instruments and those they only allow one fixed needle length [6].

Microneedling pens were developed to overcome variations in pressure and penetration depth that occur with derma rollers. Dermapen was one of the first microneedling pens available. It is an automated micro needling device with 9-12 disposable needles that operate in a stamp-like manner. Disposable needles allow the device to be reusable; therefore it is more economical than derma rollers as it can be used on different patients [7]. There are many more microneedling pens now available and currently in development.

Principle of PCI

The basis of microneedling is the controlled, mechanical stimulation of the normal wound healing response. Microinjuries within the dermis stimulate the recruitment of platelets and neutrophils. This in turn stimulates the release of transforming growth factor-alpha (TGF- α), TGF-beta (β) and platelet-derived growth factor (PDGF), which all facilitate propagation of the extracellular matrix (ECM). During the proliferation phase, growth factors continue to be released and influence monocytes, keratinocytes, and fibroblasts, resulting in the formation of a fibronectin matrix and deposition of type-III collagen. Finally, during the remodeling phase, type-III collagen is converted to type-I collagen and vascular maturation occurs. This leads to the effect of skin tightening [5].

Multiple microneedling studies have results displaying corresponding histologic enhancement that supports this mechanism. A study of 10 patients that received 6 microneedling sessions at 2-week intervals were found to have statistically significant increases in collagen types I, III, VII, and tropoelastin [8]. Another study on murine animals showed an increase in epidermal thickness and dermal connective tissue, as well as an upregulation of TGF- β , and elevated levels of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) [9].

Another hypothesis to explain percutaneous collagen induction is through creation of trans-epithelial potentials (TEPs) by MNs. MNs penetrate the skin and create soft tissue injury that activates the Na/K-pump to re-establish the intra- and extra-cellular electrical potential that was created during injury. This causes Na⁺ ions to be transferred out of the cell while K⁺ ions are transferred into the cell. As cells experience repeated penetration by MNs, it causes cells to remain in a permanent active state that leads to a polarized electro-magnetic field (EMF) in the intercellular electrolyte. This EMF stimulates DNA expression in surrounding cells that eventually leads to gene expression of proteins and growth factors that facilitate healing [10].

Drug Delivery Mechanism

Microneedling has been explored as a means of drug delivery. The stratum corneum (SC) is the principal barrier for penetration of drugs. Average thickness of the SC is 10 μ m, but it may vary greatly based on location and hydration status. By creating micropores through the SC and into underlying epidermis, microneedling bypasses the barrier function of the SC to rapidly deliver topical medications into the dermal microcirculations without penetrating deep enough to stimulate nerves within the dermis thus causing pain. Choice of MN becomes important, as bleeding induced by longer needles has been hypothesized to inhibit drug absorption [11].

Transepidermal water loss (TEWL) is used as a surrogate of barrier dysfunction, comparing percentage increase of relative humidity at the procedure site to baseline prior to MN application. Two studies by Kalluri H et al. [12], first using dissolvable maltose MN apparatus followed by stainless steel Derma Roller, in hairless rat skin models demonstrated significant increase in TEWL following MN application with return to baseline barrier function by 4hrs [12,13]. Both studies used methylene blue stain and calcein imaging to assess micropore size and closure time. Micropore size was influenced by MN base diameter, length, and material with wider, longer, and stainless steel MN creating larger pores. Time to complete micropore closure was directly related to micropore size with a range of 12 to 18hrs. Micropore closure, TEWL elevation, and overall barrier dysfunction can be prolonged up to 72 hrs by application of occlusive dressing, such as plastic film [12]. Gupta J et al. [14] used electrical impedance spectrometry in human subjects to confirm the effect of occlusion on skin permeability. Additionally this study demonstrated the benefit of quick reversal and return to baseline skin permeability following removal of occlusive dressings [14]. It is thought that occlusion inhibits lamellar body mediated epidermal recovery by artificially restoring barrier function [13]. Occlusive dressings benefit MN drug delivery by extending transport time while maintaining potential for rapid correction of skin barrier function, mitigating harmful effects of barrier breakdown.

Microneedling Applications in Dermatology

Skin rejuvenation

Percutaneous collagen induction therapy has been used for skin rejuvenation. In one study, 10 female patients with upper lip wrinkles underwent two treatment sessions with microneedling. 30 weeks after treatment, the patients had a mean 2.3-fold reduction in wrinkle severity using the Wrinkle Severity Rating Scale (WSRS) and 33% reduction in skin irregularity demonstrated by skin replicas [15].

Another study found that 6 microneedling sessions at 2-week intervals produced noticeable clinical improvement of photo aged skin in 10 patients with Fitzpatrick skin type III and IV and Glogau class II to III wrinkles. Importantly, there was corresponding histologic enhancement with statistically significant increases in collagen types I, III, VII, and tropoelastin [8].

Microneedling with fractional radiofrequency (MFR) is a type of ablative resurfacing combined with microneedling that has also been studied for skin rejuvenation. This modality utilizes insulated microneedle electrodes that deliver radiofrequency energy to the dermis without damaging the overlying epidermis [16]. This creates thermal zones in the deeper reticular dermis and thus induces long-term dermal remodeling which includes ne elastogenesis and neocollagenesis [17]. In a split-face trial with 15 females, one side of each subject's face was treated with MFR alone, and the other side was treated with MFR plus stem cell conditioned medium. After 3 treatments, both sides showed improvement in hydration, melanin, erythema index, and skin roughness. Histologic exam revealed marked increase in dermal thickness and dermal collagen content [18].

Platelet-rich plasma (PRP) combined with microneedling has been studied extensively. One study with 113 patients who received an average of 1.5 sessions found statistically significant improvements in wrinkle effacement and skin laxity by Patient and Observer Satisfaction Scores at 12 months. Interestingly, this same study found

similar results when using microneedling alone [19].

Acne scars

Treatment of post-acne atrophic scars is a frequent indication for microneedling and has been widely studied. Microneedling alone has been found to be effective for treatment of rolling, boxcar, and pitted scars [20]. Microneedling combined with glycolic acid peel [21]; platelet-rich plasma, vitamin C [22] and subcision with 15% trichloroacetic acid [23] were all more effective for treatment of post-acne atrophic scars than microneedling alone. It has been found to be safe and effective for all skin types with minimal risk of hyperpigmentation [23,24].

Non-acne scars

Microneedling has been shown to be effective for burn scars and varicella scars in several case reports. In a case report by Cho et al. [25], a Korean woman with a facial burn scar achieved significant improvement in texture and contracture when treated with combined microneedling and carbon-dioxide laser [25]. Significant improvement was also reported in treating varicella scars in a Fitzpatrick skin photo type V girl, with no hyperpigmentation or other complications [26]. In another study, 16 patients being treated for post-burn scarring reported their improvement as a mean of 80% or better than before treatment. Histologic examination revealed considerable increase in collagen and elastin deposition 12 months postoperatively [27].

Acne vulgaris

MFR has been studied for treatment of active acne vulgaris. In a study of 18 patients with Fitzpatrick skin type IV with moderate to severe acne vulgaris who were treated with two sessions of MFR at 1-month intervals, 16 showed objective clinical improvement in number and severity of inflammatory acne lesions, scar improvement, enlarged facial pores, skin tone, and texture [28]. In another study in which 20 Korean patients with acne vulgaris received a single full-face MFR treatment, the casual sebum level and sebum excretion rate showed 30-60% and 70-80% reduction after 2 weeks post treatment and remained below baseline until week 8 [16]. In a prospective clinical trial, 25 patients with moderate to severe acne were treated with MFR. Results showed number of acne lesions (inflammatory and non-inflammatory) decreased, though inflammatory lesions responded better than non-inflammatory lesions [29].

Hyperpigmentation

Microneedling has been used to treat hyperpigmentation, such as melasma and periorbital hypermelanosis. In a study of 20 patients, patients treated with combined skin needling and depigmenting serum (with active ingredients rucinol and sophora-alpha) showed a statistically significant reduction in Melasma Area Severity Index (MASI) score and luminosity index levels compared to the side treated with depigmenting serum alone, and clinical symptoms were significantly improved [30]. A RCT of 60 patients with moderate to severe melasma compared tranexamic acid (TA) microinjections to microneedling followed by application of topical TA. In the microinjection group, there was 35.72% improvement in the MASI score compared to 44.41% in the microneedling group, at the end of the third follow-up visit. Six patients (26.09%) in the microinjections group, as compared to 12 patients (41.38%) in the microneedling group, showed more than 50% improvement [31]. In a case study by Sahni, a photo type V man with significant idiopathic periorbital melanosis had good to excellent reduction in periorbital melanosis

with the Derma Frac™ device, which combines microneedling with simultaneous infusion of a serum containing active ingredients. Physician global assessment revealed 50% to 75% and 75% to 90% improvement, after 4 and 12 sessions, respectively [32]. Another study of 13 female patients treated for periorbital melanosis found combining 10% trichloroacetic acid and microneedling demonstrated a fair, good, or excellent response in 92.3% by both Physician and Patient Global Assessment [33].

Alopecia

Research has also shown that microneedling can be beneficial for treatment of alopecia. In a study of 100 men with androgenic alopecia, two randomized groups were formed, one received minoxidil alone and the other received microneedling combined with minoxidil. After 12 weeks of treatment, hair count was significantly greater in the microneedling group and 82% of patients in this group reported more than 50% improvement versus only 4.5% of patients in the minoxidil alone group [34]. Similar results were found in a case series in which four men resistant to finasteride and minoxidil added 6 months of microneedling to their therapy [35]. In a case study of two patients with alopecia areata, combined treatment with microneedling using a derma-roller and triamcinolone acetonide showed clinical improvement with each session and excellent hair growth 3 weeks after three treatments [36].

Hyperhidrosis

MFR has been studied for treatment of hyperhidrosis. In one study, twenty patients with primary axillary hyperhidrosis (PAH) underwent 2 sessions of bipolar MFR treatment at 4-week intervals. Hyperhidrosis Disease Severity Scale (HDSS) scores decreased significantly after the first and second months of posttreatment follow-up sessions. In a subjective assessment, 70% of patients expressed more than 50% improvement in their sweating. The starch-iodine reaction was also remarkably reduced in 95% of patients. Histological findings showed a decrease in the number and size of both apocrine and eccrine glands 1 month after the final treatment [37]. Naeini et al. [38] had similar results in a study of twenty-five patients with severe PAH who underwent three sessions of MFR at 3-week intervals in which one side was treated with MFR and the other was sham controlled. The HDSS and VAS demonstrated significant improvement after treatment on the treated side in comparison with the control side [38].

Drug delivery

Microneedling has also been shown to augment transdermal drug delivery. In a case series we reported successful treatment of large recalcitrant plantar warts when combining microneedling with topical bleomycin. We observed a 100% cure rate in three patients after an average of 4 treatments. The treatment was associated with decreased pain, decreased risk of side effects, and increased ease in covering large surface areas versus using intralesional bleomycin [39].

Microneedling to facilitate lidocaine topical anesthetic delivery has also been studied. Lidocaine-coated solid microstructure transdermal systems (sMTS) provide rapid, targeted dermal delivery of lidocaine. Rapid onset anesthesia was seen in a recent study using lidocaine-coated sMTS with 53.3% efficiency at 1 min and 71.1% at 4 min according to a recent study [40]. Wear time paralleled drug delivery with adequate levels reached within minutes, vastly superior to conventional topical lidocaine application for clinical or emergency procedures.

Photodynamic therapy (PDT) utilizing the photosensitizers aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) has been efficacious and shown excellent cosmetic outcomes when treating actinic keratosis, superficial BCC, SCCs, and other sun-related skin damage [41]. A split-face study demonstrated superior improvement on global score, mottled pigmentation, fine lines, roughness, and shallowness with MN-assisted MAL-PDT application at 30 and 90 days compared to the conventional MAL-PDT side. Mean time for resolution of side effects lasted 10 days on the MN-assisted side versus 5 days with conventional PDT [42]. As efficacy of PDT is dose dependent, increased responsiveness in MN-assisted PDT is likely due to increased penetration of photosensitizing agents into the epidermis and dermis normally limited by the SC [42].

Additionally, 5-fluorouracil (5-FU) utilizing a microneedling delivery system may have potential in the management of SCC is. Topical application and intralesional injection of 5-FU are well documented in the literature as effective non-surgical treatment strategies in SCC is, specifically in challenging anatomical locations or in the presence of multiple lesions when surgery is not optimal [43]. Both methods have limitations. Delivery of 5-FU in combination with microneedling allows for precise, concentrated drug delivery of chemotherapeutic not obtainable from topical application without subjecting patients to routine, painful intralesional injections. Intralesional injection of 5-FU is also complicated by persistent erythema, induration, and erosion at the site of injection [44,45]. Further investigation by the authors is underway to confirm the benefit and efficaciousness of 5-FU MN delivery in SCC is.

Adverse Effects

Microneedling is a safe procedure with a low rate of adverse effects. The most commonly reported adverse effects include post-procedure erythema and irritation, although these are transient and usually resolve within a few hours [46]. Post-inflammatory hyperpigmentation has been reported in patients with Fitzpatrick skin photo types of III or greater [11,20]. Tram-track scarring has also rarely been reported [47].

There are two case reports of more serious adverse effects of microneedling. One case report describes two sisters who developed systemic hypersensitivity to microneedling treatment, possibly related to the needles themselves [48]. Another case series reports 3 patients who developed foreign-body type facial granulomas following microneedle therapy with topical vitamin C. The study proposes that topical products prior to microneedling can introduce immunogenic particles into the dermis and potentiate local or systemic hypersensitivity reactions [49]. The product used by these patients was not authorized for or designed for intradermal injection, and is the reason for the severe adverse effects. Thus, it is imperative that only chemicals approved for intradermal injection should be used in combination with microneedling.

Conclusion

Microneedling has been explored for the treatment of a wide variety of dermatologic conditions. This review serves as a primer for dermatologists and highlights the encouraging results of studies reporting the benefit of microneedling in skin rejuvenation, acne scars, non-acne scars, acne vulgaris, hyperpigmentation, alopecia, and transdermal drug delivery. These studies report clear benefits with minimal side effects. As the use of microneedling becomes more widespread, it is important to increase the number of randomized,

controlled trials to provide further data on the efficacy and safety of microneedling.

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