

Retinoids: Literature Review and Suggested Algorithm for Use Prior to Facial Resurfacing Procedures

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ABSTRACT

Vitamin A-containing products have been used topically since the early 1940s to treat various skin conditions. To date, there are four generations of retinoids, a family of Vitamin A-containing compounds. Tretinoin, all-trans-retinoic acid, is a first-generation, naturally occurring, retinoid. It is available, commercially, as a gel or cream. The authors conducted a complete review of all studies, clinical- and basic science-based studies, within the literature involving tretinoin treatment recommendations for impending facial procedures. The literature currently lacks definitive recommendations for the use of tretinoin-containing products prior to undergoing facial procedures. Tretinoin pretreatment regimens vary greatly in terms of the strength of retinoid used, the length of the pre-procedure treatment, and the ideal time to stop treatment before the procedure. Based on the current literature and personal experience, the authors set forth a set of guidelines for the use of tretinoin prior to various facial procedures.

KEYWORDS: Facial resurfacing, retinoic acid, retinoids, tretinoin

INTRODUCTION

The quest for more youthful, younger-looking skin is of paramount concern amongst the ageing population. Reversing the visible signs of skin ageing, such as wrinkles, pigmentation and lack of elasticity, is of importance to a woman's quality of life. These reasons represent a common reason for seeking a dermatologic referral.^[1,2]

Retinoids are a family of compounds derived from Vitamin A. First-generation agents include both retinol and tretinoin. These compounds have been used topically and systemically since the 1940s for various skin conditions, particularly acne. Over a quarter century ago, female acne patients reported that their skin subjectively felt smoother and had less wrinkles after treatment with retinoid-containing products. In the 1980s, Kligman *et al.* first published a report showing that tretinoin rejuvenated the epidermis.^[3-6]

Subsequently, a clinical trial proved that patients treated with tretinoin had improvement in sunlight-induced epidermal atrophy and dyspigmentation.^[4] Tretinoin has since become the gold standard for the treatment of photoaged skin.^[7,8]

In addition to prolonged sun exposure, numerous other intrinsic factors, such as diabetes and hypothyroidism, have been shown to cause epidermal atrophy, reduced fibroblast proliferation and decrease matrix synthesis.^[9] Lateef *et al.* demonstrated that these effects can be reversed with retinoid treatment, specifically noting an increase in epidermal thickness and collagen production.^[10] Ultimately, the Food and Drug Administration (FDA) has approved the use of tretinoin for photo-damaged skin. Retinol, a metabolic precursor of tretinoin, is also widely

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included in multiple over-the-counter “anti-wrinkle” cosmetic products.

Despite the FDA approval, the use of tretinoin and retinol-containing products are associated with certain adverse effects. These side effects include pruritus, burning sensation, erythema and desquamation. Collectively, this side effect profile is termed the “retinoid reaction” and is more common with the use of tretinoin than with retinol.^[3,8,11] The retinoid reaction is dose dependent and subsides over time.^[3,8]

For patients who are sensitive to tretinoin-containing products or with a severe retinoid reaction, the use of an adapalene, marketed under the brand name of Differin, may be used as there is a lower incidence of retinoid dermatitis. Adapalene is a third-generation retinoid with many of the same properties as tretinoin. However, unlike tretinoin, adapalene is a synthetic compound with a longer half-life. This longer half-life causes a delay in maximal effectiveness and requires an earlier initiation period for adapalene prior to resurfacing procedures.^[12-14]

In contrast to the irritancy potential of the classical, prescription tretinoin therapy, cosmetic anti-wrinkle formulations using retinol are well tolerated.^[15] Despite the literature being devoid of studies directly comparing tretinoin to retinol, it is presumed that retinol anti-wrinkle products are not as clinically efficacious as prescription strength tretinoin therapies.^[15,16] Therefore, the question remains: What is the optimal dosing and duration of topical tretinoin application prior to facial resurfacing procedures?

MECHANISM OF ACTION

Retinoids’ primary action is on the upper papillary dermis where collagen content is increased by collagen degradation inhibition. Topical tretinoin increases Type I collagen production by 80% in photoaged skin and increases wrinkle effacement through epidermal hyperplasia with compaction of the stratum corneum and thickening of the granular layer.^[3,17] Tretinoin binds to specific nuclear receptors thereby inducing a conformational change and exposing a DNA-binding site. The activated nuclear receptor controls cellular function by binding to specific DNA sites that can either stimulate or repress gene expression. When bound, tretinoin produces a 70% repression of AP-1 transcription factor binding to DNA. This repression decreases the overall activation of metalloproteinases.^[18-21] Likewise, matrix metalloproteinase production and collagen degradation are prevented with topical treatment of tretinoin prior to ultraviolet irradiation.^[22]

RETINOID THERAPY

Multiple studies within the literature have sought to determine the optimal concentration of tretinoin to balance its beneficial and deleterious effects. The standard treatment dose of tretinoin cream is 0.05%, applied nightly. This administration protocol shows an improvement in fine wrinkle effacement in approximately 3 months.^[8,23] Changes in the dermal layer were seen after 12 months of continued treatment, at which point new collagen fibre formation and elastic material reduction were seen, histologically.^[23]

To date, there have been two randomised, controlled, double-blinded studies performed with both studies showing a more significant improvement in epidermal wrinkle effacement using a 0.05% over a 0.01% concentration of tretinoin.^[24,25] In other studies, 0.1% was compared with a 0.025% concentration of tretinoin and followed over an 8-month period. In looking at epidermal changes, no statistically significant difference was seen between the two concentrations.^[3,26] Other studies have investigated lower tretinoin concentrations for longer durations. Olsen *et al.* studied the daily application of 0.05% and 0.01% versus a placebo for 11 months. Statistically significant improvements of both concentrations over the placebo were seen.^[27] Nyirady *et al.* studied the daily application of 0.02% and 0.05% tretinoin cream for 24 months and found no statistically significant difference in clinical outcomes.^[28] In a porcine model, Hung *et al.* treated eight animals with 0.05% tretinoin cream daily for 10 days prior to partial-thickness skin wounding. This study concluded that continued treatment with topical tretinoin before wounding caused an acceleration of epithelial wound healing but continued treatment after wounding retarded reepithelialisation.^[29]

Other studies have looked at higher concentrations of tretinoin cream for shorter durations. Kligman *et al.* noted that the use of 0.25% tretinoin cream, used every other night for 14 days, yielded similar clinical and histological improvement after 4–6 weeks that a 0.05% concentration did after 12 months.^[30] This use of higher concentrations over a shorter course of therapy was later termed ‘rapid retinisation’.^[31] Multiple other studies noted that discontinuation and/or truncation of tretinoin therapy resulted in the reversal of the epidermal effects.^[32-34]

Retinol-containing products have been in use, cosmetically, since 1984.^[1] The use of retinol was widely accepted after Kang *et al.* published a study showing that retinol induces epidermal thickening in a similar manner as retinoic acid, but with minimal side effects, unlike tretinoin.^[35] Retinol causes less transepidermal water loss, irritancy, erythema and scaling compared

to tretinoin. Likewise, clinical studies proved retinol's relative capacity in monotherapy to produce fine wrinkle effacement.^[36-38]

CLINICAL STUDIES

Chemical peel

The depth of dermal injury is what classifies chemical peels into a superficial peel, medium peel or deep peel. Superficial peels, such as alpha-hydroxy acids, beta-hydroxy acids and Jessner solution, injure the epidermal layer without deeper penetration. Medium peels, trichloroacetic acid (TCA) 20–35%, penetrate into the papillary dermis. Deep peels, including phenols with or without croton oil and TCA 45–50%, affect the reticular dermis.^[18,39]

Hevia *et al.* studied the effects of pretreatment with 0.1% tretinoin cream, used 14-day prior to a 35% TCA peel of the face. The reduced stratum corneum caused by the tretinoin cream application resulted in earlier, more intense, frosting, and a statistically significant increase in reepithelised skin area after 7 days.^[40]

Kim *et al.* used guinea pig skin to show morphological and histological changes with tretinoin pretreatment prior to a TCA chemical peel. The peak epidermal hypertrophy occurred after 7 days of tretinoin application. This hypertrophy climax was shown to reverse towards normal epidermis after 14 days of continued treatment.^[41]

Dermabrasion and microdermabrasion

Microdermabrasion utilises inert aluminium oxide or sodium chloride crystals to debride the superficial epidermal layer. Unlike other resurfacing procedures, dermabrasion can be performed on all skin types to address photodamage, superficial rhytides, hyperpigmentation and/or scarring.^[39,42,43] Surgical dermabrasion usually involves the use of a power-driven rotating diamond rasp where the skin is pared mechanically. Depth is determined by the operator and can vary from superficial epidermal to deep reticular dermal. The technique is not often used because of the risk to operative personnel by skin and blood aerosolised by the procedure.

In one study, patients were pretreated using 0.5% tretinoin cream for 14 days prior to undergoing either a full or half-face dermabrasion. These pretreated faces were completely reepithelialised 2 days earlier than the control group.^[44] These findings were further solidified in an animal model, wherein animals pretreated with tretinoin attained reepithelialisation earlier than their control counterparts, both clinically and histologically.^[21,45]

Laser

Laser resurfacing comes in three forms: Ablative, non-ablative and a combination of ablative and non-ablative. Within these categories, the energy can be delivered either as full-field or fractionated. Ablative lasers penetrate into the dermis and treat fine and deep rhytids, telangiectasias, actinic keratosis and scarring. Such ablative lasers include the carbon dioxide and erbium: yttrium-aluminium-garnet lasers.^[39,46-53] Non-ablative lasers include the long pulse dye, pulsed pulse dye, pulsed potassium titanyl phosphate, erbium: yttrium-aluminium-garnet, diode and erbium laser. These lasers heat the tissue without ablating, thereby having a more favourable side effect profile compared to the ablative lasers.^[54-56] Fractional lasers whether ablative or non-ablative deliver thermal injury in columnar zones leaving untouched tissue in between. This avoidance of confluent injury allows for faster recovery with a reduced side effect profile when compared to the full-field lasers.^[57,58]

Animal studies were conducted looking at the effects of pretreating guinea pigs with tretinoin prior to undergoing carbon dioxide laser resurfacing. This tretinoin pretreatment resulted in faster reepithelialisation and healing.^[59] Despite these results, Orringer *et al.* showed no benefit in terms of reepithelialisation when pretreating photo-damaged forearm skin with 0.05% tretinoin cream.^[60] This is likely due to the fact that after 21 days of tretinoin treatment, only the epidermis is affected, which is ablated by carbon dioxide resurfacing.

DISCUSSION

The question remains, "Do all facial resurfacing procedures necessitate skin pretreatment with tretinoin?" Each resurfacing modality causes various levels of dermal injury. Harnessing the technical ability to control the level of injury while performing these resurfacing procedures is paramount for efficacy and safety. Stegman proved histologically that the rate of reepithelialisation is proportional to the depth of injury caused by the resurfacing procedure.^[19] Therefore, the use of tretinoin would provide the most benefit when used prior to therapies that cause deep wounds when compared to those procedures that cause only superficial epidermal injury.

In regards to retinoid dermatitis, the best prevention method when using higher strength retinoids is to start treatment at a lower concentration and gradually increase the concentration. The concomitant use of skin moisturisers also helps hydrate and protect the skin from a dermatitis reaction. Furthermore, synthetic retinoids such as adapalene and tazarotene may be used in patients with sensitivity to tretinoin. Likewise, retinoids can be

safely used in darker skin types, Fitzpatrick Type IV+, in the same manner as with lighter skin types. Gel or solution formulations may be of benefit for very oily skin types while creams are better for drier skin types.^[4,25,34,61-65]

Pretreatment with tretinoin products has been deemed essential to expedite reepithelialisation and epidermal healing; however, much of this seems to be based on anecdotal evidence. Pretreatment regimens have varied greatly in terms of the strength of tretinoin used, length of the pre-procedure treatment and ideal time to stop treatment before the procedure.^[20,21] We, therefore, have derived tretinoin pretreatment guidelines prior to specific facial resurfacing procedures.

Recommendations

Based on the available literature exploring the mechanism of action of tretinoin, as described above, as well as published observational studies and personal experience, we propose the following algorithm for the pre-operative use of tretinoin in facial resurfacing [Figure 1]. For ablative lasers, the authors recommend using 0.1%

tretinoin cream applied nightly for 3 months prior to, and discontinuing 24 h before, the planned procedure. For non-ablative laser resurfacing, this dose should be decreased to 0.05%. Tretinoin pretreatment is not recommended for microdermabrasion since this procedure only affects the superficial epidermis. A 0.1% tretinoin concentration pretreatment is recommended for a surgical dermabrasion, with initiation starting 3 months prior to the planned procedure date.

In regard to chemical peel resurfacing, tretinoin concentration recommendations are divided into three categories, depending on the level of depth of the peel. For a superficial chemical peel, it is recommended to use a 0.05% concentration, starting 1 month prior to the procedure, daily and halting 24 h before the treatment. For a medium chemical peel, use a 0.1% concentration daily starting 1 month prior to the procedure and discontinuing 24 h prior to the chemical peel. A deep chemical peel requires the use of 0.1% tretinoin concentration, daily, starting 3 months prior to the procedure and stopping 24 h prior.

Retinoid pretreatment algorithm

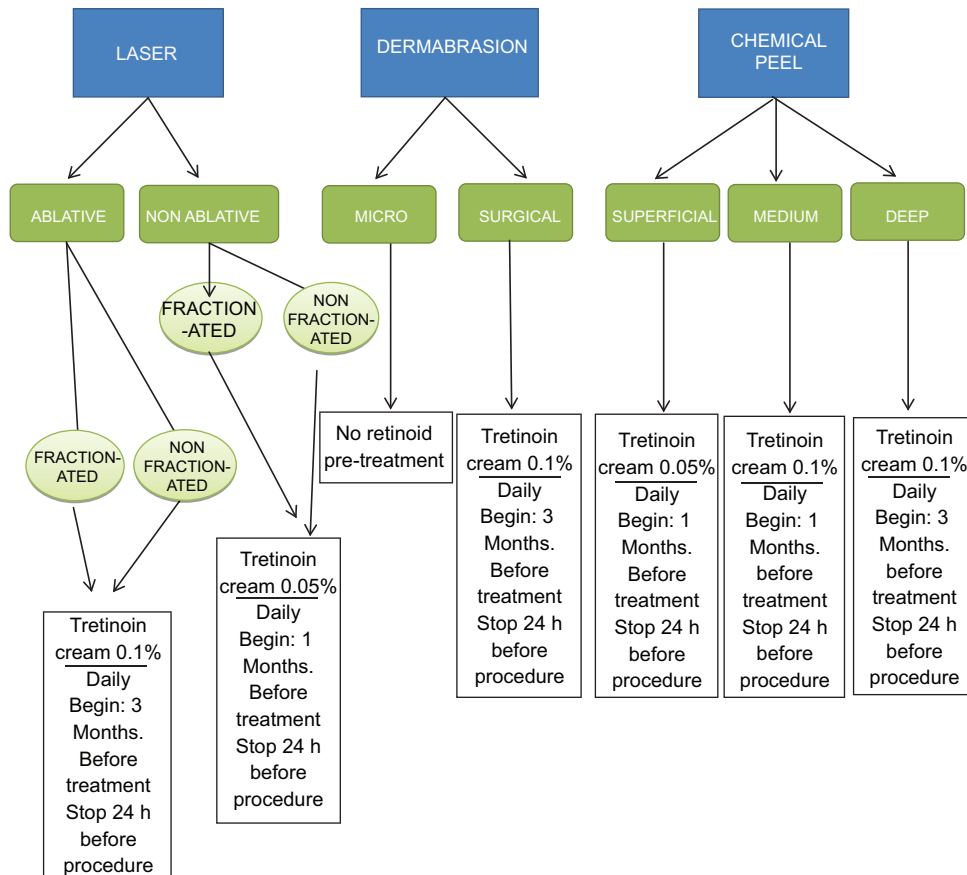


Figure 1: Tretinoin pretreatment recommendations prior to laser, dermabrasion and chemical peel facial resurfacing

To date, no data within the literature support the notion that discontinuing the use of tretinoin prior to a resurfacing procedure is deemed necessary. However, the authors recommend not starting the use of tretinoin-containing products sooner than 3–4 weeks prior to a facial resurfacing procedure. Treatment with products containing tretinoin initiated within 3–4 weeks of a resurfacing procedure causes symptomatic dryness and exfoliation as the facial skin has not yet had time to accommodate to its effects. Likewise, the improvement in fine wrinkle effacement reverses once tretinoin application ceases, and therefore, there are no data available that show usage of these products leading into a resurfacing procedure interferes with healing.

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Conflicts of interest

There are no conflicts of interest.

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