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Clinicopathological Aspects and Risks of the Phenol Croton Oil Peel

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Abstract

Background: Phenol/croton oil is a unique chemical formulation promoting deep skin resurfacing and cellular renovation. Even though it has been used for decades in Plastic Surgery, the clinicopathological features, as well as the risks related to phenol/croton oil clinical application have not been thoroughly studied. The aim of this study was to assess the effectiveness of the phenol/croton oil peel, the pathological characteristics and the emerging potential risks.

Methods: Sixty-four patients were treated with phenol/croton oil peel between 2014 and 2023; 21 of them underwent resurfacing at their oral area (upper/lower lips), one underwent resurfacing at their lower eyelid wrinkles, 22 patients full face resurfacing, two patients were treated for their acne scars and additional four for multiple body seborrheic keratosis.

Results: The wrinkles, as well as the acne scars were dramatically improved in all patients, the seborrheic keratosis was eliminated, while adverse events and undesired clinical manifestations related to the peel intervention were mild and reversible for all patients.

Conclusion: The application of phenol/croton oil constitutes a very powerful tool for deep chemical peeling and facial skin rejuvenation, nevertheless it should be used cautiously due to its potential complications.

Keywords: Phenol; Croton oil; Deep chemical peeling; Skin aging; Wrinkles; Acne scars; Keratosis

Introduction

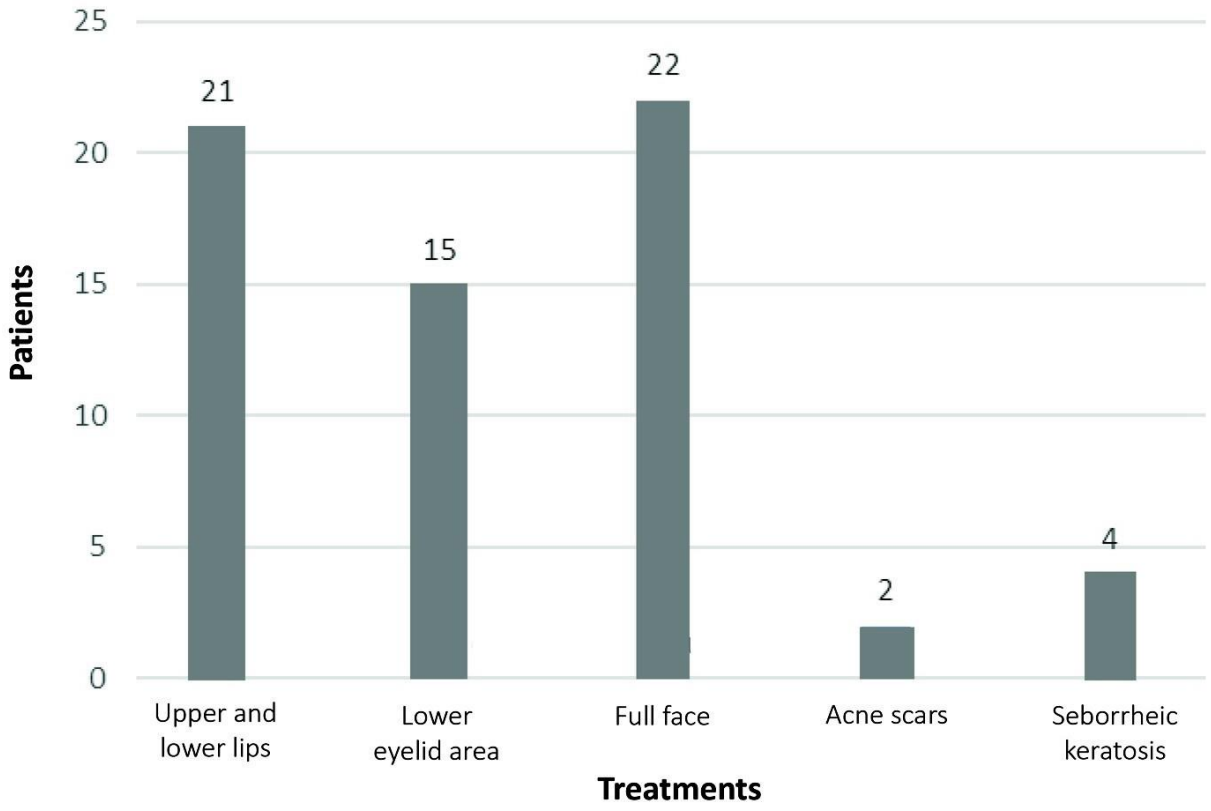
Wrinkles or skin dyschromias can be accelerated by aging, sun exposure, smoking or hormonal changes [1]. Chemical peelings exfoliate the skin and can be divided into superficial, medium and deep ones; they can be applied to treat the whole face or they can be used at the lips improving the "smoker lines", the lower eyelids "softening" the fine wrinkles, the upper eyelids improving the skin laxity, etc. Superficial peels brighten the skin: the more acidic the peel is, the deeper the penetration will be. The main types of superficial peelings involve A-Hydroxy Acids (AHA), like glycolic/lactic acid and B-Hydroxy Acids (BHA), like salicylic acid, while "Jessner's" solution with ethanol is broadly used [2]. These peelings are considered to be safe, without any apparent risks and can be applied to all skin types [3]. Medium peels include TCA (Trichloroxic Acid) 10-35% (alone or mixed with superficial peels) and phenol 80%. The TCA permeates the epidermis stratum corneum and exfoliates the skin; it treats actinic keratosis and improves fine wrinkles, pigmentary changes and/or acne scars [2]. Finally, there are several types of deep peels: TCA 50% and over and phenol/croton oil constitutes some of them, while mechanical dermabration and CO_2 or Erbium-YAG lasers present similar results. Phenol/croton oil peels are well known since the ancient times [2] and can treat atrophic/pox-like acne scars, solar lentigines, seborrheic keratosis, "Bowen disease" and angiosarcomas; they have been used as sclerosing agents or for chemical matrixectomy, as well as for the treatment of stable vitiligo and alopecia areata [3]. Despite their effectiveness, there are certain risks related to their use, especially in patients with dark and/or thin skin. Phenol (carbolic acid or phenolic acid) acts as a local anesthetic and disinfectant [2]. It can be neutralized by glycerin or adequate amounts of water and plays a key role in "Baker-Gordon's formula", together with croton oil [4]. Baker published their formula in 1961, consisting of croton oil, phenol and septisol; septisol is a standard emulsifying agent regulating the phenol permeation, due to its keratolytic properties. T h e "Baker-Gordon's" formula was the cornerstone of deep chemical peels for decades and phenol is its main active ingredient [4-8]. In 1996, Hetter proved croton oil as the more critical agent of the "Baker-Gordon's" formula, and since then, the "Hetter's formula" is the gold standard for the deep peels [9]. Croton oil derives, as an extract, from the seeds of the "Croton tiglium" plant (Euphorbiaceae family) and its medical applications have been well recognized since the early 19^{th} century. It boosts the phenol's activity, coagulating the keratin, increasing the site's vascularization [2]. Using higher concentrations of croton oil allows using lower concentrations of phenol, thereby reducing the systemic effects of phenol toxicity in the formula. Hetter's work demonstrated that a 0.2% increase of croton oil concentration increases the phenol peel activity by 20%. Despite their effectiveness, risks and adverse events related to phenol/croton oil peels should always be considered. Phenol coagulates and penetrates in 2-3 mm into the skin, therefore, it is systemically absorbed 15 min after its application [7]. It has to be avoided when there is a renal/kidney medical history because its absorption can lead to kidney malfunction [6]. In all cases, patients have to be adequately hydrated to help phenol excretion from the urinary system [8]. Cardiac toxicity like tachycardia and premature contractions may appear in 7% of all phenol/croton oil cases, while in severe ones, they could lead to atrial fibrillation. However, when the serum phenol clears, the premature contractions are eliminated and the cardiac rhythm reverts to normal. The inherent

risk of cardiac arrhythmias comprises the main safety concern for phenol/croton oil peels and can be avoided by dividing the face into 6-8 units and spacing the application of phenol to each unit 15-20 min apart **[10]**. Close follow up by monitoring, hydration and sufficient air exchange at the operating room have to be considered when phenol/croton oil peels are performed at larger areas. Patients on antihypertensives and/or antidepressants should be given short acting beta-blockers, such as propranolol, to reduce the risk of arrhythmias (if there is no chronic obstructive pulmonary disease, like asthma, severe bradycardia and advanced atrioventricular blocks). Eyes irritation is on risk during the deep peel application, so eyes must be closed before the procedure. The erythema appears after the croton oil/phenol peel normally, starting the first week and reaching a peak the second week after application: the deepest the penetration/efficacy of the peel, the more extensive the erythema will be. Prolonged erythema is more likely to occur in dark skin patients and thin skin areas, like the eyelids or the neck and the mandible **[4]**. Acne and milia, small white cysts, contact dermatitis or infection may also be developed, mainly due to Staphylococcus spp, Streptococcus spp and Pseudomonas aeruginosa **[11]**, but they are in short term or they can be easily treated by close follow up after croton oil/phenol application. The aim of this study was the assessment of the clinical effectiveness of the phenol/croton oil peel, the evaluation of the relevant pathological characteristics and the emerging potential risks for the patients.

Methods

Sixty-four patients treated with phenol/croton oil peel between 2014 and 2023. Twenty-one performed resurfacing at the oral area (upper/lower lips), fifteen at their lower eyelids, twenty-two patients performed full face treatment, while two patients were treated for their acne scars and an additional four for the multiple seborrheic keratosis around their back and lumbar region **(Table 1)**.

Table 1: Treatments (phenol/croton oil peels) applied to 64 Caucasian patients (60 female and 4 male).



We applied "Hetter's" 1.2% croton oil solution for perioral peel; 0.8%, 0.4% and 0.1- 0.2% croton oil, were used for the cheek/forehead, temporal regions, eyelids and neck, respectively. The 0.8% croton oil solution consisted of 5.5 ml water, 0.5 ml septisol (Delasco, Council Bluffs, IA), 2ml phenol 88% (Delasco, Council Bluffs, IA) and 2ml stock solution (containing 24 m l phenol and 1ml croton oil, Delasco, Council Bluffs, IA) **[9]**. Specific care was given to the periorbital area, since the application of concentrations higher than 1% croton oil, increases the risk of hypopigmentation **[12]**. All patients signed an informed consent and all procedures were performed by the same Plastic Surgeon. The patients' mean age was 53 years (range 33-75 years), while mean follow-up was 2 years. All patients were female except four male patients (one with acne scars and three treated at the lower eyelids) **(Table 1)**. Patients with heart, kidney, and hepatic history or a medical background of keloid, smoking, recent use of isotretinoin, psychological imbalance and Fitzpatrick skin types IV-VI were excluded from the study. The skin was cleaned with alcohol 70% prior to application and the phenol/croton oil peel was applied by gauze/cotton pads. Topical anesthesia was applied, with sensory facial nerve blocks with xylocaine/epinephrine in addition to the anesthetic properties of the phenol solutions. All patients were fully monitored and IV hydrated **[13,14]** When a full face peel was applied, the face was subdivided into six aesthetic units. Initially, the peel was administered to the forehead, followed by the right and the left cheek, perioral and periorbital area, and finally the nasal and mental region. Assessing the endpoint of the croton oil/phenol peel was crucial: a white frost was observed immediately after the peel, followed by a fine gray color and, finally, by a mild pink color at the skin; the peel penetration increased proportionally to the number of passes, the pressure applied and the croton oil concentration **[15]**. Different facial areas presented different penetrations; the perioral skin was thicker than temporal and eyelid areas. Hair growth was not compromised by phenol/croton oil, and the

peel was safely applied at the hairy areas of the beard and eyebrows and scalp **[16,17]**. An oral analgesic treatment (ibuprofen tablets) was administered three times daily, during the first 3 days of the treatment application, while a sulfadiazine cream was applied every 2-6 hours, during the first 8-10 days, in order to hydrate, disinfect **[18]** and reduce the erythema **[8]**. In case of herpes or viral infection history, oral valacyclovir 500mg was administered for 10-14 days, starting from the first day after the peel application. Finally, following the sulfadiazine cream application **[19]**, a sun-care cream was used on a daily basis, along with a modified "Kligman's" formula (tretinoin 0.1% + hydroquinone 5% + hydrocortisone 0.1% + Vitamin C 5%), for at least 15 days to eliminate the skin erythema **[20]**.

Results

Photographic evaluation was performed for all patients **(Photos 1-4)**. The mean re- epithelialization period was 10-15 days, while significant improvement was demonstrated in all 64 patients; two patients appeared with prolonged erythema and were treated with modified "Kligman's" formula. Biopsies were taken 6 months after the Phenol/Croton oil peel at the eyelids, to establish the diagnosis and comparison with the non-peel area. Histopathologic findings of the Phenol/Croton oil peel skin **(Figures 1-4)**, demonstrated reepithelization, mild perivascular and periadnexal, lymphocytic infiltrations and vasodilation (probably due to the regeneration properties of the peeling). Interestingly, in the pathology report there was evidence of large quantity of new collagen, deposited in bands beneath the dermis. To our knowledge, this is the first histopathological report of a Phenol/Croton oil patient.

Photo 1: Patients before and 3 months after full face phenol/croton oil peel.

Photo 2: Patient before and after phenol/croton oil peel at her upper/lower lip areas.

Photo 3: Patient before and 6 months after a full-face phenol/croton oil peel.

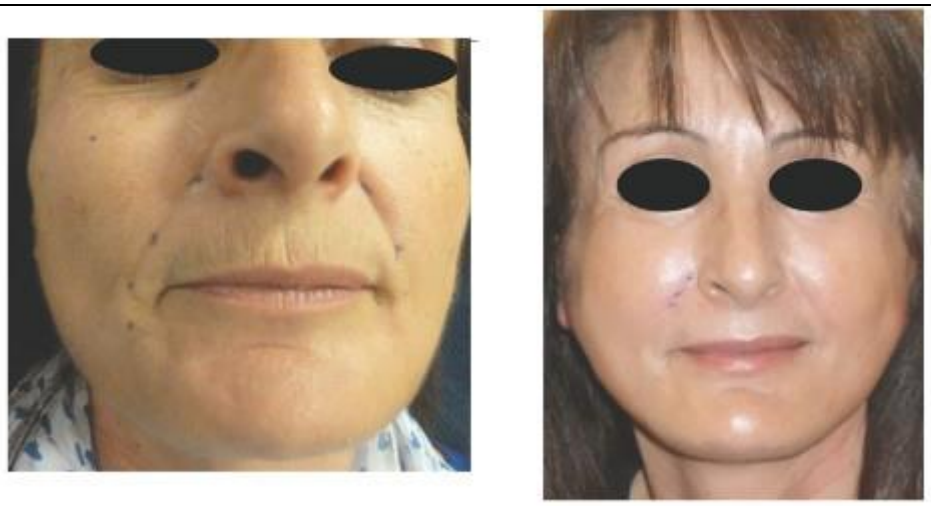


Photo 4: Patient before and 8 months after face lift and phenol/croton oil peel at her lower eyelids/upper lip.

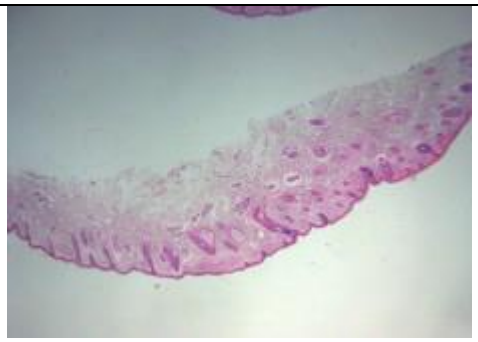


Figure 1: Histopathologic findings prior to Croton oil peel 1.25X.

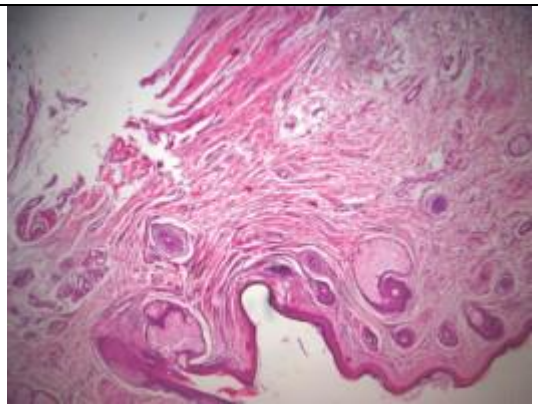


Figure 2: Histopathologic findings prior to Croton oil peel 4X.

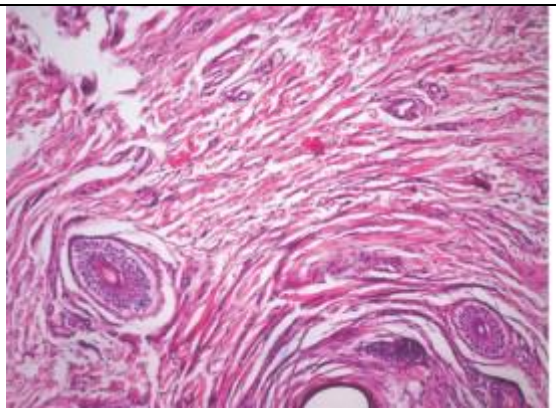


Figure 3: Histopathologic findings after Croton oil peel 10X.

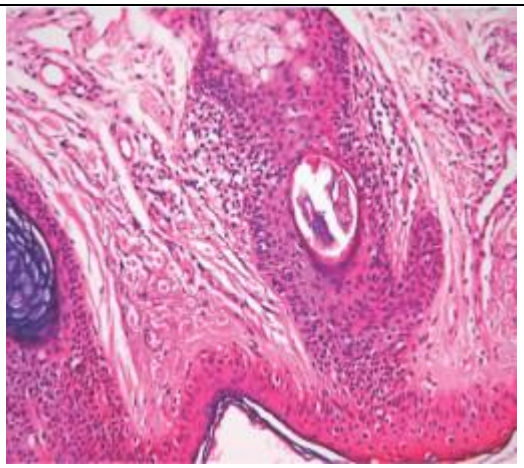


Figure 4: Histopathologic findings following Croton oil peel 40X, showing reepithelization, mild perivascular and periadnexal, lymphocytic infiltrations and vasodilation.

Discussion

Skin peels vary between non-invasive methods, like the application of milk and honey, and more invasive ones, like the application of mustards, sulfur, lemon and even fire, since the ancient times [21]. At the early of 20th Century, facial peels were popularized, while after the Second World War they were widely used to reverse facial aging [22]. Chemical peels are divided to superficial, medium and deep, depending on the skin

penetration, the concentration of the solution applied, the treatment duration and the application method. Superficial peels result in partial thickness chemical burn and can be subdivided into very light and light ones [23]. The very light superficial peels, that reach the outer skin, include A-Hydroxy Acids (AHAs), B-Hydroxy Acids (BHAs) (like salicylic acid), Trichloroacetic Acid (TCA) 10-20% and vitamin A. The light superficial peels, like Glycolic Acid (GA) 40-70%, TCA 25-30% combined, occasionally with Jessner solution, penetrate deeper. Superficial peels lead to skin regeneration, while they treat acne and post inflammatory erythema, mild photoaging, actinic keratosis, solar lentigines and skin dyschromias [23]. Medium peels, including TCA 30% and phenol 80%, penetrate to the upper dermis and effectively treat superficial rhytids or photoaging. Deep peels reach the mid-reticular dermis to treat severe dyschromias and deep rhytids. All chemical peelings may pose a considerable risk. Skin type assessments using Fitzpatrick's scale and photodamage degree using Glogau's scale should be thoroughly monitored. Superficial peels are considered to be safer, while medium and deep peels should be cautiously applied, especially to Fitzpatrick's types IV-VI patients, due to their post-inflammatory or prolonged erythema properties [24]. The pretreatment with tretinoin enhances the penetration of medium to deep peels, while the application of bleaching formulas eliminates the possibility of dyschromias [24]. Smoking, immunosuppression, bad nutrition, cardiac, renal or hepatic history, isotretinoin use ≤6-8 months before the procedure compound risk factors for systemic toxicity and poor healing; history of herpes complex requires prophylactic treatment [25]. The deep chemical peels can treat melasma, actinic or seborrheic keratosis, deep facial wrinkles, acne scars, as well as onychomycosis. TCA 50% may require multiple treatments, while laser resurfacing by CO_2/Erbium-YAG can lead to scarring or persistent erythema (especially the CO_2). The necessary equipment is also very expensive to obtain. Dermabrasion can be an optimal choice for resurfacing due to lower cost and considerable efficacy, however it requires a long learning curve [26]. Subsequently, there is a need for an alternative peel strategy. The application of phenol implies a chemical burn with extension to the upper-reticular dermis (helping new collagen formation). It has been used to treat deep wrinkles [27], while histological studies demonstrated subdermal collagen proliferation [28]. Phenol whitens the skin and balances the pigmentary changes; it can treat severe acne scars, xanthelasma, actinic/seborrheic keratosis and actinic cheilitis. When used alone, 80% phenol solutions act as a medium-depth peel penetrating to the upper reticular dermis [23]. The addition of septisol minimizes deeper tissue injury, while the addition of limited amounts of croton oil to any concentration of phenol leads to deeper peels. "Baker-Gordon's" peel consisted of 3 mL of 88% phenol, 3 drops of croton oil, 2 ml of distilled water, and 8 drops of septisol, resulting in a phenol concentration of 49%. In this formula, phenol is believed to be the main active agent; low concentrations of phenol penetrate deeper compared to higher ones and appear to be more toxic. Septisol causes a comparatively deeper penetration, while croton oil is viewed as an irritant. These facts have been widely accepted and remained unchallenged during the last 30 years [7]. Multiple formula variations have been described since then, including buffered phenol peels, glycerin use instead of septisol, and variations in the concentration of phenol and croton oil [29]. Stone PA [8] described a modified formulation of phenol peel proposing that croton oil is responsible for the depth of peel and skin depigmentation. In Hetter's formula [9], croton oil contained a powerful cytotoxic substance and established as the active ingredient; septisol was added to cause deeper tissue injury and the peel depth increased with higher concentrations of croton oil and repeated applications of the solution, managing the complications of phenol. Wambier et al. [26] demonstrated, as well, that the "Baker-Gordon's formula" exhibited similar clinical effects with Hetter's formula, however, Hetter's peel appeared to

be safer, due to increased Post- Inflammatory Hyperpigmentation (PIH) in the "Baker-Gordon's" peel. Risks of the phenol use involve cardiac arrhythmias, milia, hypertrophic scar or keloid formation, post-inflammatory hyperpigmentation or hypopigmentation, erythema, infection, pallor or abnormal healing **[27]**. There is prolonged recovery from transudate, crusting and edema similar to partial/full thickness skin burn. The depth of the peel is reflected to the recovery period and is influenced by skin thickness and the concentration of the solution. The application of "light croton oil" concentrations led to a 10-12 days healing period, while more concentrated solutions required a comparatively prolonged healing period, exceeding 12 days in most patients of this study. Following local application, phenol is absorbed systemically through skin penetration, undergoes liver biotransformation and is, finally, being excreted by the kidneys. Potential risks and adverse events include respiratory distress and cardiac arrhythmias, so it's very critical to moderate the complications of the phenol application with increased concentration of the croton oil. Cardiac monitoring and adequate hydration throughout the procedure, as well as intervals of at least 15 min between sequel aesthetic courses **[27]**, eliminated the risk of cardiac arrhythmias in our patients. Avoiding peeling of dark and thin skin patients and applications in areas like eyelids or mandible is crucial to prevent scars **[17]**; male patients with thicker skin are safer to treat **[6,10]**, while female patients should be peeled more cautiously. Edges of the peels were feathered 1-2 cm to the surrounding skin in our patients, particularly at the mandibular borders, to prevent lines of demarcation. A hydration cream containing antibiotic applied after the treatment can minimize possible infection or skin dehydration **[28-30]**; we used sulfadiazine cream which is safer than occlusive tape, allowing us to have a close follow up of the patient.

Conclusion

Additional studies are needed to elucidate the full clinical and pathological aspects of phenol/croton oil peels, compared to other deep peels, ablative lasers, radiofrequency applications or dermabrasion. Phenol/croton oil peel stimulates new collagen formation; it can disrupt the keratin bonds and the cellular structure, producing a new skin frame with less wrinkles. Despite its clinical advantages, close follow up is required at the post-peel period due to its potential risks.

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