Original Article

Cryotherapy versus Phenol Chemical Peeling for Solar Lentigines: A Clinical, Histologic, Immunohistochemical and Ultrastructural Study

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Background. Solar lentigines are the most common benign sun induced lesions. Their management includes chemical peeling and cryotherapy. **Objective.** to compare cryotherapy to phenol chemical peeling in treatment of solar lentigines. **Patients and methods.** Twenty patients with solar lentigines on the dorsa of hands underwent liquid nitrogen spray cryotherapy of the right hand lesions for 3-5 seconds and focal Baker-Gordon phenol peeling of the left hand lesions. **Results.** Cryotherapy to 181 solar lentigines resulted in complete disappearance of 26 lesions (14.35%), marked improvement of 18 (9.95%), moderate improvement of 86 (47.5%), mild improvement of 44 (24.3 %), and bad response in 7 (3.9 %), while phenol peeling to 158 lesions resulted in complete disappearance of 49 lesions (31.02 %), marked improvement of 36 (22.78%) and moderate improvement of 73 (46.2%) (p value = 0.001). Higher patient`s satisfaction was shown with phenol peeling but with more pain, prolonged healing time and more prolonged erythema. Histological and immunohistochemical assessment revealed normalized epidermis with phenol peeling and only markedly reduced melanocytes with cryotherapy. Electron microscopic examination revealed small dark melanin granules with some aggregated complexes in melanocytes and keratinocytes with cryotherapy. However, with phenol peeling, small dispersed melanin granules, mostly with light melanization were present. **Conclusion.** Our results suggested phenol peeling to have better results due to acting on both melanocytes and keratinocytes, normalizing their proliferative and melanization properties. However, by "cryo-peeling" comparable results could be achieved. *(J Egypt Women Dermatol Soc 2010; 7: -)*

Keywords. Cryotherapy, phenol chemical peeling, solar lentigines

Solar lentigines (actinic lentigo, senile lentigo, sun spots, liver spots or age spots) are the most common benign hyper-pigmented sun induced lesions, that occur in sun exposed areas; face, arms, dorsa of the hands and upper part of the trunk. Although these lesions are most common in individuals aged 30 - 50 years, they are now seen in younger individuals, because of their increased exposure to sun tanning, and the use of artificial sources of ultraviolet light (UV)[1]. Solar lentigines possibly occur due to melanocytes mutation which results in proliferation and enhanced pigment production in response to UV radiation. Moreover, it is possible that there is a genetic susceptibility to the development of solar lentigo in response to acute or chronic UV radiation and that melanocytes in these circumscribed proliferations are permanently altered[2].

Cryotherapy has been used to treat skin lesions for approximately 100 years. Liquid nitrogen is currently the most widely used cryogen. It may be considered the first line therapy for treatment of solar lentigines, because of the susceptibility of melanocytes to freezing with liquid nitrogen (melanocytes freeze at -4 to -7°C), whereas squamous cells resist injury at -20°C[3].

Phenol peeling is an example of deep chemical peeling, in which there is necrosis followed by regeneration of the epidermis and papillary dermis that extends to the reticular dermis. Phenol was used long time ago in treatment of pigmented lesions such as melasma, freckles and solar lentigines, since it is known to be toxic to melanocytes[4,5]. The aim of this work was to compare between the effect of cryotherapy and chemical peeling with phenol in treatment of solar lentigines, clinically, histologically, immunohistochemically and on basis of ultrastructural changes.

PATIENTS AND METHODS

The study included 20 patients attending the Dermatology Outpatient Clinic of Ain Shams University Hospitals complaining of solar lentigines, 7 males (35%) and 13 females (65%), 47 - 70 years

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Conflict of interest. None declared.

old with mean age 57 ± 6.92. The skin phototypes according to Fitzpatrick skin phototyping[6] were: II for 2 patients (10%), III for 8 patients (40%) and IV for 10 patients (50%). Glogau photoaging classification[7] was II for 5 patients (25%) and III for 15 (75%). Solar lentigines varied in size between patients (from 3 mm up to 1 cm) and varied in colour from light to dark brown. All patients were subjected to clinical evaluation including: history with attention to smoking and occupations and/ or hobbies with excessive sun exposure, duration of the lesions, relation to sun exposure, previous therapies, history of relevant medical conditions e.g. photosensitivity, keloids, hypertrophic scarring, post-inflammatory hyper-pigmentation, diabetes mellitus, heart disease, liver disease, renal disease, cold intolerance and connective tissue diseases, relevant surgical history including dermabrasion and laser surgery and previous or present relevant medication such as systemic retinoids, oral anticoagulants and oral contraceptive pills. Complete general and dermatological examination and a screening blood chemistry including blood urea nitrogen, creatinine, and liver enzymes were done.

Patients with pregnancy and lactation, local infection in the area to be treated, history of systemic retinoid therapy within 12 months before the study, current administration of contraceptive pills or oral anticoagulants, severe systemic diseases e.g. renal failure, liver cell failure, heart failure, significant immunosuppresion, uncontrolled diabetes mellitus and connective tissue diseases, history of medical diseases which contraindicate cryosurgery such as; cold intolerance, cold urticaria, Raynaud`s disease and history of allergic reactions to cryosurgery, were excluded from the study.

All the 20 patients underwent treatment with cryotherapy of the lesions of the right hand and phenol peeling of the lesions of the left hand. Photographic documentation was done before the treatment, and 6 weeks after treatment. Photographs were taken using identical camera setting and lighting by a Sony DSC-S700 digital camera.

Punch biopsies were taken from 5 skin lesions before and 3 weeks after treatment (after complete re-epithelialization). Skin biopsies were divided into two halves: the first half was fixed in 10% buffered formalin and sectioned in 5 µm sections for routine hematoxylin and eosin (H&E) and immunohistochemical staining, and the other half was used for electron microscopic examination.

Methods

Right-sided cryotherapy

Liquid nitrogen spray technique was used by Cry-Ac gun (Brymill, Witney, Oxon, U.K.). The nozzle tip of the spray gun was held about 1 to 1.5 cm from the treatment site, a single freeze-thaw cycle (FTC) was allowed, and liquid nitrogen was sprayed on the lesion until ice ball formation had spread from the centre to include a margin of <1mm around the lesion (3 - 5 seconds). When this was achieved, freezing was stopped and the site was permitted to thaw spontaneously. The patient was advised to put local antibiotic cream (fusidic acid 2%), and to take analgesic if the pain was intolerable.

Left-sided phenol chemical peeling

Focal deep chemical peel was done using classic Baker-Gordon formula which is composed of 3 mL of United States Pharmacopeia (USP) phenol (88%), 2 mL of tap water, 8 drops of liquid soap, and 3 drops of croton oil. We instructed patients to drink a liter of fluids before the session to promote metabolism and excretion of phenol. Since we treated the lesions focally, neither anesthesia nor analgesia was needed. The skin of the area to be peeled was degreased with alcohol. Phenol was applied strictly to the lesion with cotton tipped applicator. The end point occurred when the skin showed white frosting. Finally, a layer of zinc oxide paste was applied. Patients were advised to keep the peeled area moist to promote wound healing, by emollient application (zinc oxide paste), and to apply topical antibiotic (fusidic acid 2%). Patients were instructed to take analgesic if the pain was intolerable, and to use sunscreens (SPF 50 - 60).They were also instructed not to pick during the recovery period.

Clinical evaluation

Clinical evaluation of the treated lesions was done through comparing patient′s photos before and after treatment. Improvement was classified into: no improvement: <20% lightening (grade 0; G0), mild improvement: 20%-49% lightening (G1), moderate improvement 50%-75% lightening (G2), marked improvement >75% lightening (G3), and complete disappearance of the lesions 100% (G4). Patient′s satisfaction after the treatment was judged according to the rapidity of healing and response, and was classified into: no satisfaction, minimal satisfaction, moderate satisfaction and great satisfaction.

Histologic examination

Histologic examination was carried out on standard H&E sections. Solar lentigines showed significantly elongated club-shaped or tortuous rete ridges, composed of deeply pigmented basaloid cells intermingled with melanocytes[8].

Immunohistochemical staining

Immunoperoxidase technique was used for demonstration of melanocytes. Sections were dried in a 50°C oven for 30 minutes, de-paraffinized in xylene, re-hydrated using a series of alcohols (100%, 90%, and 85%), and washed in PBS (pH 7.4). Endogenous peroxidase was blocked with 0.5% H_2O_2. Antigen retrieval treatment was performed

by boiling in 10 mM citrate buffer solution (pH 6) for 20 minutes followed by cooling at room temperature for 20 minutes. After blocking with normal serum (Lab Vision Corp., Fremont, CA), the slides were incubated with MART-1/Melan-A rabbit monoclonal antibodies (Lab Vision- cat. RB- 9054-R7-Ready to use), for 32 minutes at room temperature, then with a secondary biotinylated primary antibody, and finally with avidin-biotin-peroxidase complex. Hematoxylin was used as counter-stain. Melan-A gave brown cytoplasmic immunoreactivity in melanocytes.

Electron microscopy

Biopsy specimems were fixed in 3% buffered glutaraldehyde for 2 hours at 4˚C and then washed with the cacodylate buffer solution (pH 7.3) for 15 minutes at 4˚C. This was followed by post-fixation in 1% buffered osmium tetraoxide, dehydration in ascending grades of ethyl alcohol, and embedding in Epon 812. Sections were prepared using Nova ultramicrotome and stained with uranyl acetate and lead citrate, and examined under JEOL 100C-X (JEOL Ltd., Tokyo, Japan) transmission electron microscope. Lesional basal keratinocytes contained increased melanosomes and melanosome complexes (polymelanosomes), which formed massive caps on the nuclei. Even in the upper layers of the epidermis, including the horny layer, numerous melanosomes are present, largely in a dispersed state rather than as complexes[9].

Statistical analysis

Statistical analysis of the results was done using Statistical Package for the Social Sciences (SPSS) version 12 program. Comparison between both modalities as regards clinical response of patients was done using Mann-Whitney test. Results in relation to gender were analyzed using Student`s *t* test and results in relation to Fitzpatrick skin type and Glogau`s photoaging classification were done using ANOVA and Student`s *t* test respectively. Comparison between both modalities as regards patient's satisfaction was done using Chi-square test. Results were considered significant when *p* value was ≤0.05, and highly significant when *p* value ≤ 0.001.

RESULTS

Clinical assessment

Our study included 20 patients underwent treatment with cryotherapy on solar lentigine lesions of the right hand and phenol peeling on the lesions of the left hand. Pain was a common complaint in all patients. Pain during phenol chemical peel was intense burning, and was greater than that during cryotherapy and lasted for 4-6 hours after the session. However, with cryotherapy the pain was less intense and lasted no longer than 15 minutes after the session.

Comparison between both modalities revealed statistically matched results in all patients except in 6 patients; number 1, 6, 9, 10, 16 and 17, in whom phenol chemical peeling showed statistically significant better response (p value 0.001, 0.001, 0.0016, 0.001, 0.006, and 0.001 respectively) (Table 1). Collectively, cryotherapy was applied to 181 solar lentigines lesions and resulted in bad response (G0) in 7 (3.9 %) of the lesions, mild improvement (G1) of 44 (24.3 %), moderate improvement (G2) in 86 (47.5%), marked improvement (G3) in 18 (9.95%) and complete disappearance (G4) in 26 (14.35%) of the lesions. On the other hand, phenol chemical peeling was done to 158 lesions and resulted in moderate improvement (G2) in 73 (46.2%) of the lesions, marked improvement (G3) in 36 (22.78%) and complete disappearance (G4) in 49 (31.02 %) of the lesions. Thus, phenol chemical peel showed an overall better clinical response as the results showed a statistically highly significant difference (*p* value = 0.001) (Table 2). Figure 1 illustrates the clinical response of both modalities in one patient.

As regards patient's satisfaction with cryotherapy: 2 patients (10%) reported no satisfaction, 7 (35%) reported minimal satisfaction, 8 (40%) expressed moderate satisfaction and 3 (15%) expressed great satisfaction. With phenol chemical peel we found that: no patients (0%) were not satisfied, 4 patients (20%) expressed minimal satisfaction, 8 (40%) expressed moderate satisfaction and 8 (40%) expressed great satisfaction. Comparison between both modalities revealed no statistically significant difference (*p* = 0.114).

Both modalities showed statistically matched response in both males and females using *t* test (*p* = 0.584 for cryotherapy and *p* = 0.357 for phenol peeling). The response grades to either modality in relation to Fitzpatrick skin photo-type, and Glogau's photoaging classification showed no statistically significant difference (*p* = 0.899 and 0.985 for cryotherapy, and 0.842 and 0.387 for phenol peeling respectively).

With cryotherapy, we found that blistering was minimal or not at all. The post-healing time in the lesions which developed blisters was within 1 week, while it took 3 weeks with phenol chemical peel in all lesions. Only prolonged erythema (more than 2 months) occurred in 3 patients at sites of phenol chemical peel (2 patients with type III and 1 patient with type IV Fitzpatrick skin). No other complications occurred with either technique.

Table 1. Comparison between the results of both treatment modalities as regards clinical response of patients using Mann-Whitney Test.

Patients No	Treatment	No. of lesions	Response range	Median grade	Mean rank	*z*	*p* value	
P1	cryo peeling	13 14	G0 - G4 G4 - G4	G1 G4	8.615 19.000	-3.969	0.001**	HS
P2	cryo peeling	7 5	G2 - G4 G2 - G4	G4 G2	7.429 5.200	-1.232	0.218	NS
P3	cryo peeling	14 9	G2 - G4 G2 - G2	G2 G2	12.964 10.500	-1.457	0.145	NS
P4	cryo peeling	8 6	G2 - G4 G2 - G4	G2 G3	6.750 8.500	-0.931	0.352	NS
P5	cryo peeling	8 3	G2 - G4 G2 - G4	G4 G4	6.125 5.667	-0.264	0.792	NS
P6	cryo peeling	14 22	G1 - G1 G2 - G4	G1 G4	7.500 25.500	-5.422	0.001**	HS
P7	cryo peeling	5 4	G2 - G2 G2 - G2	G2 G2	5.000 5.000	0.000	1.000	NS
P8	cryo peeling	6 4	G2 - G2 G2 - G4	G2 G2	5.000 6.250	-1.225	0.221	NS
P9	cryo peeling	8 5	G1 - G2 G2 - G4	G2 G4	5.125 10.000	-2.419	0.016*	S
P10	cryo peeling	16 20	G1 - G1 G2 - G3	G1 G3	8.500 26.500	-5.612	0.001**	HS
P11	cryo peeling	6 5	G2 - G3 G2 - G3	G3 G2	7.167 4.600	-1.476	0.140	NS
P12	cryo peeling	8 7	G2 - G4 G2 - G4	G2 G4	6.875 9.286	-1.225	0.221	NS
P13	cryo peeling	5 6	G2 - G2 G2 - G2	G2 G2	6.000 6.000	0.000	1.000	NS
P14	cryo peeling	15 10	G2 - G4 G2 - G2	G2 G2	14.333 11.000	-1.746	0.081	NS
P15	cryo peeling	6 4	G2 - G4 G2 - G4	G2 G2	5.667 5.250	-0.267	0.789	NS
P16	cryo peeling	4 6	G1 - G1 G2 - G3	G1 G3	2.500 7.500	-2.739	0.006**	HS
P17	cryo peeling	16 12	G0 - G3 G3 - G3	G2 G3	10.000 20.500	-3.765	0.001**	HS
P18	cryo peeling	6 4	G2 - G3 G2 - G4	G3 G2	6.000 4.750	-0.707	0.480	NS
P19	cryo peeling	10 8	G2 - G3 G2 - G4	G2 G2	9.000 10.125	-0.510	0.610	NS
P20	cryo peeling	6 4	G2 - G3 G2 - G3	G2 G3	4.667 6.750	-1.225	0.221	NS

*$p \leq 0.05$ is significant

**$p \leq 0.01$ is highly significant

NS = Non significant

S = Significant

HS = Highly significant

Table 2. Comparison between the total results of both modalities as regards clinical response of patients using Mann-Whitney Test.

Treatment	No. of lesions	Response range	Median grade	Mean rank	*Z*	*p* value
Cryo	181	G0 - G4	G2	136.57	7.167	0.001**
Peeling	158	G2 - G4	G3	208.30		(HS)

***p* ≤0.01 is highly significant

HS = Highly significant

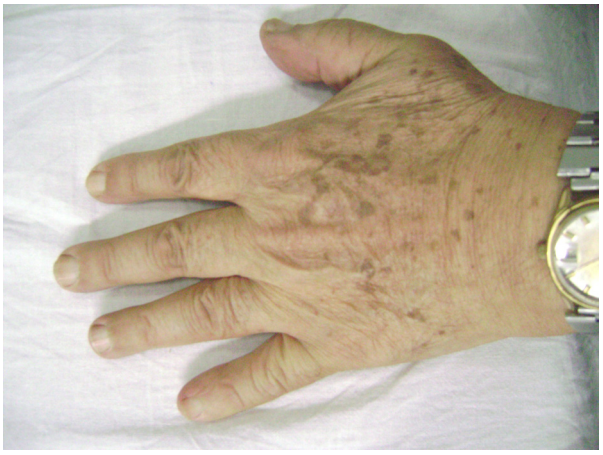

Figure 1A. Before phenol peeling: 22 solar lentigines on left hand.

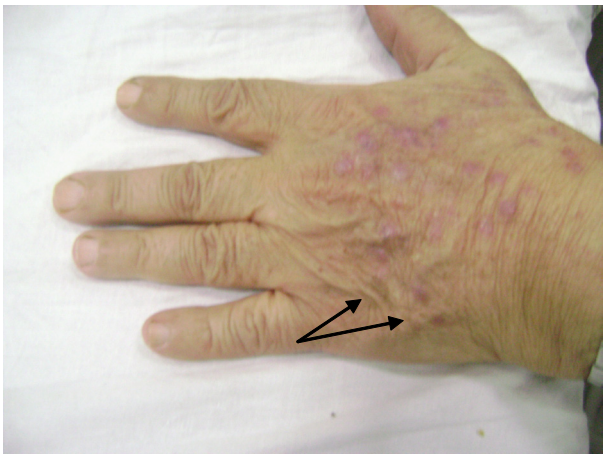

Figure 1B. After 6 weeks of phenol peeling: 16 lesions (G4) but with occurrence of persistent erythema, and 6 lesions (G2) (arrows).

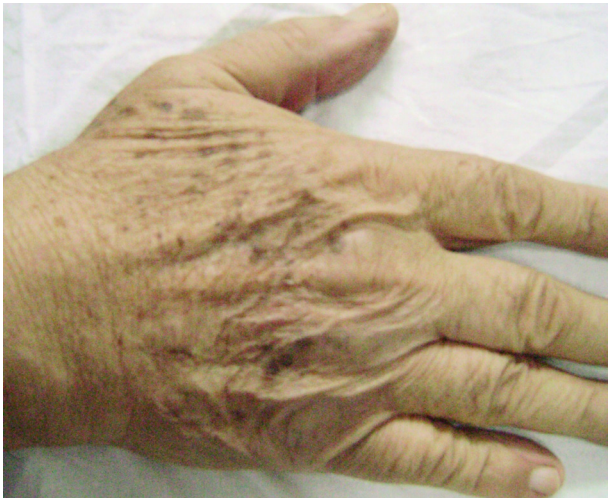

Figure 1C. Before cryotherapy: 14 solar lentigines on right hand.

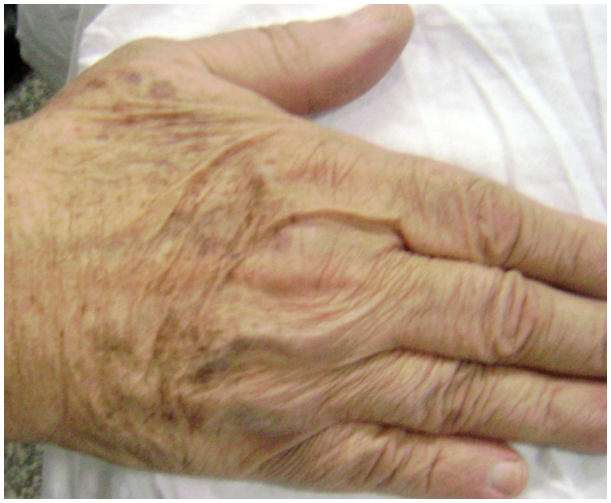

Figure 1D. After 6 weeks of cryotherapy: all lesions (G1).

Histologic and immunohistochemical assessment

Solar lentigine lesions showed club-shaped elongated rete ridges composed of deeply pigmented basaloid cells intermingled with melanocytes (Figure 2A). Melan-A staining showed that melanocytes were significantly increased in number (Figure 2B). Following cryotherapy, the rete ridges were still elongated with bud-like extensions, but pigmentation was markedly reduced (Figure 2C). Melanocytes were markedly reduced in number as evidenced by Melan-A immunostaining (Figure 2D). Phenol chemical peeling resulted in better arrangement of rete ridges than with cryotherapy. Although significantly reduced, pigmentation was more than with cryotherapy (figure 2E). Melan-A immunostaining revealed reduced but more melanocytes than with cryotherapy (figure 2F).

Ultrastructural assessment

Following cryotherapy, melanocytes contained small dark melanin granules, with few of them in aggregated complexes (Figure 3A, B). Keratinocytes also showed more and darker melanin granules (figure 3C), than with phenol peeling. After phenol peeling, melanocytes contained small dispersed melanin granules with different degrees of melanization; most of them had light melanin granules (Figure 3D, E). Keratinocytes also showed different melanin granules; most of them were light (Figure 3F).

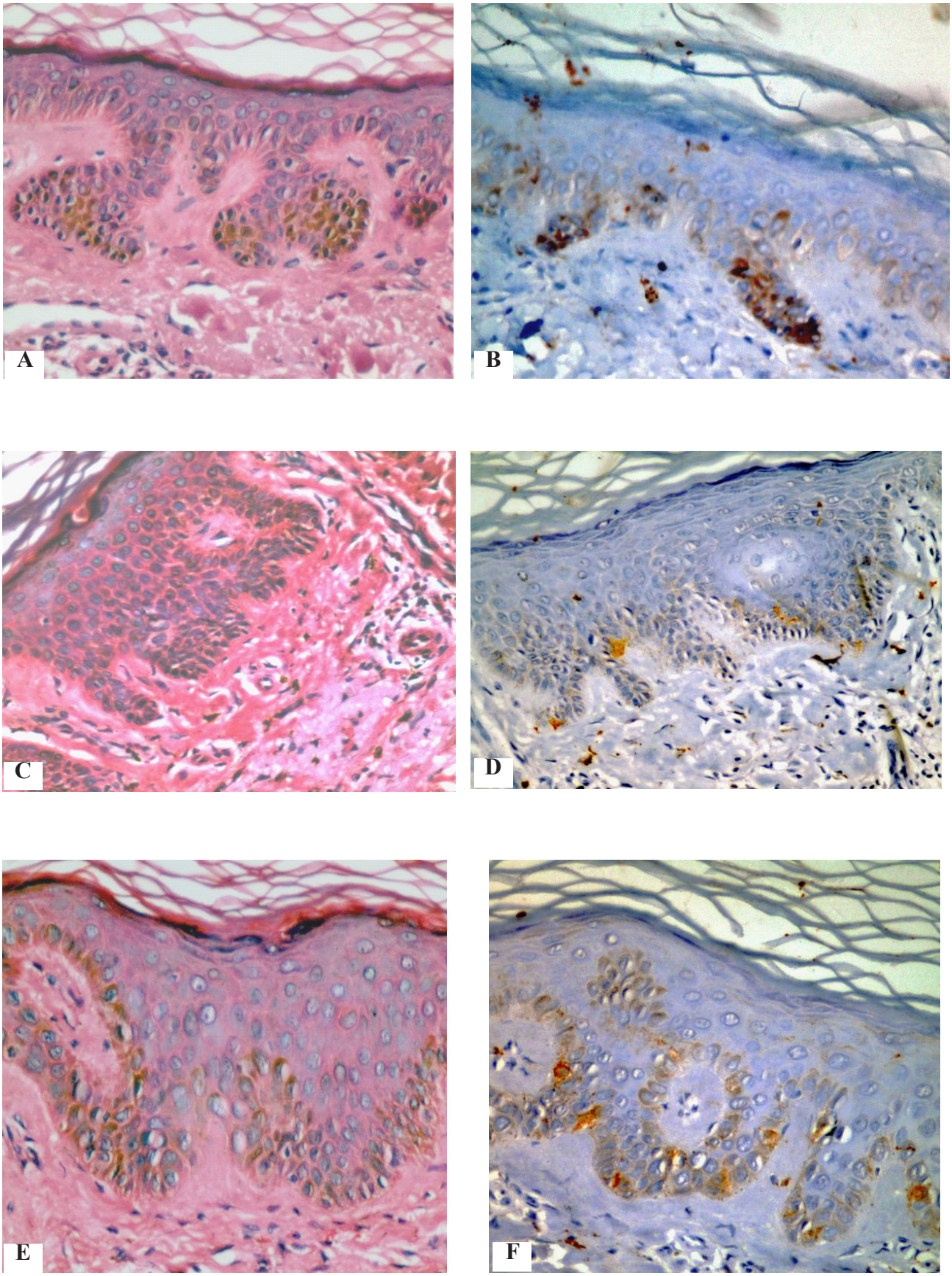

Figure 2. A: Solar lentigine before therapy (H&E x400). B: Solar lentigine before therapy (Anti Melan-A x400). C: After cryotherapy (H&E x400). D: After cryotherapy (Anti Melan-A x400). E: After phenol peeling (H&E x400). F: After Phenol peeling (Anti Melan-A x400).

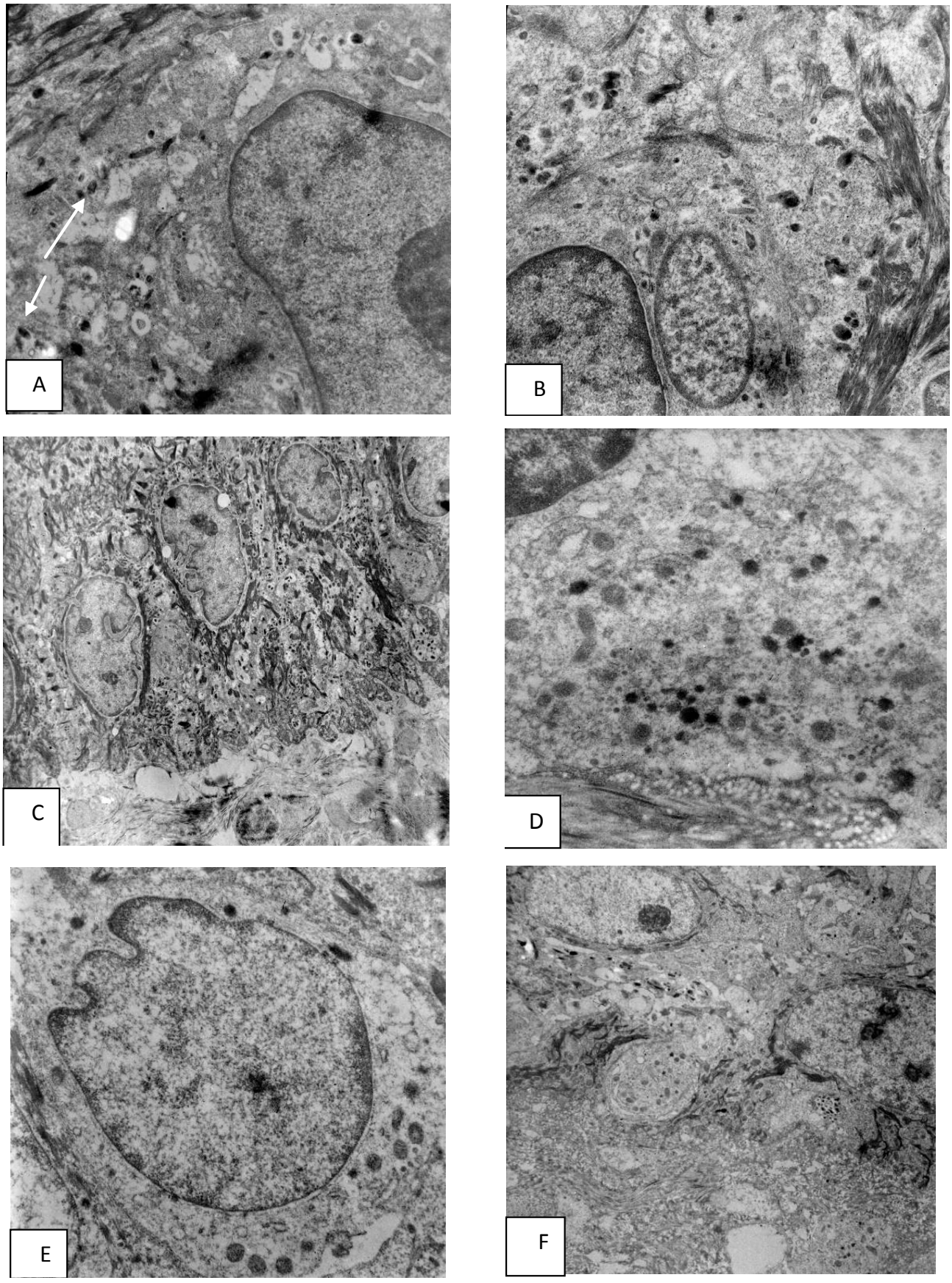

Figure 3. After cryotherapy; A: Melanocyte contains small dark melanin granules; few of them are seen in complex aggregates (marked by arrows) (EM x6000). B: Another melanocyte showing small-sized dark aggregated melanin granules (EM x8000). C: Keratinocytes with dark melanin particles (EM x1500). After Phenol peeling; D: Melanocyte contains small dispersed melanin granules with different sizes and degree of melanization; most of them with light melanization (EM x8000). E: Another melanocyte with light melanin granules (EM x8000). F: Keratinocytes with melanin particles variable in size and melanization (EM x1500).

DISCUSSION

Although benign, solar lentigines are of great aesthetical concern for the patient[1]. Many therapeutic modalities have been advocated in treatment of solar lentigines, including topical tretinoin, hydroquinone, adapalene, combination of mequinol and tretinoin, cryotherapy, chemical peels, and laser surgery[10]. Because cryotherapy and chemical peeling are accessible and cost effective treatments and have shown good results in some reports, we decided to use these modalities in the treatment of solar lentigines over the back of the hands.

Treatment of 181 lesions with 3-5 seconds of liquid nitrogen spray cryotherapy resulted in improvement 148 (81.8 %) of the lesions and complete disappearance in 26 (14.35%), with no reported complications. Eighteen patients (90%) reported some degree of satisfaction towards the results.

Zouboulis et al.[11] reported the use of a single FTC of 30 to 40 seconds nitrous oxide contact surgery in 6 patients with solitary large solar lentigo lesions (3-16 cm in diameter) for one or two sessions. Full remission of all lesions was reported with excellent cosmetic results. The discrepancy between these results and ours could be attributed to the different cryogen and our use of spray technique in a single session-based therapy only for 3-5 seconds. Almond-Roesler and Zouboulis[12] treated 20 patients with small solar lentigines with 5 or 10 seconds of liquid nitrogen contact cryosurgery. Substantial lightening was observed in 80% of patients treated for 5 seconds and 100% of patients treated for 10 seconds. Minimal skin atrophy was observed in 10% and 60% of patients treated for 5 and 10 seconds, respectively. In our study, using 3-5 seconds of spray cryotherapy resulted in substantial lightening of 96.13% of the lesions. Further studies using other techniques of cryotherapy for different durations are recommended.

Compared to Trichloroacetic acid (TCA) chemical peeling, Janer et al. [13] treated randomly 21 patients with solar lentigo on the dorsa of the hands with either TCA 30% solution or 1-5 seconds of liquid nitrogen spray cryosurgery. Cryotherapy showed better results than TCA, with no complications for any treatment, except for a small hypertrophic scar in one of the cryotherapy treated patients. Moreover, Raziee et al. [14] treated randomly 25 women with solar lentigines of both hands, with either liquid nitrogen cryotherapy by pressing cotton tipped applicator for 3-5 seconds or TCA 33% solution. Cryotherapy was more likely to produce substantial lightening of the solar lentigines than TCA 33% solution particularly in lower Fitzpatrick skin types ($p = 0.025$), but it was more painful and took more time to heal. Compared to these studies, as regards cryotherapy, we showed similar response range, but with no reported complications.

In the present study, treatment of 158 lesions with focal Baker-Gordon phenol chemical peeling resulted in improvement of all lesions with complete disappearance in 49 (31.02 %) of them. All patients expressed some degree of satisfaction to the results, but 3 patients showed prolonged erythema as a side effect after treatment. To our knowledge, no previous studies have been reported in treatment of solar lentigines with phenol chemical peel. However, Hopking et al.[15] and Piamphongsant[16] reported good results by using phenol in treatment of other pigmented lesions (congenital pigmented nevi and melasma respectively).

We found that phenol chemical peeling showed better clinical response than cryotherapy (G2-G4 in 100% of the lesions with phenol while G1-G4 in 96.13% of the lesions with cryotherapy) and higher patient's satisfaction. However, more pain, longer healing time and more complications (prolonged erythema) were reported with phenol chemical peel than cryotherapy. These results could not be compared with others. Both modalities showed statistically matched response in both males and females. In contrast, Fintisi and Landau[17] reported that thick male skin is usually less responsive to deep peel. Further studies on larger numbers of patients are needed to establish such a conclusion. Again, the response grades to either modality in relation to Fitzpatrick skin phototype, showed no statistically significant difference. Similarly, the same authors[17] reported that although the ideal patient for deep chemical peeling is a blond, blue-eyed with a fair complexion, previous experience showed that phenol-based peels could be performed on patients with olive and dark skin. We also found statistically matched results in Glogau's photoaging type II and III patients with both modalities. Glogau and matarasso[18] stated that photoaging type I is not an indication for deep chemical peeling because it may be more damaging than beneficial, while photoaging type II, III and particularly type IV may benefit from deep peeling.

Both keratinocytes and melanocytes contribute to the histopathological changes of solar lentigines. The epidermis of solar lentigo shows significantly elongated rete ridges, composed, especially in their lower portion, of deeply pigmented basaloid cells intermingled with melanocytes. The melanocytes appear significantly increased in number in some cases, but only slightly or not at all increased in others[8]. We demonstrated that both modalities reduced the number of lesional melanocytes. However, the number was reduced more with cryotherapy, compared to phenol peeling. Nevertheless, elongated tortuous rete ridges were less reduced by cryotherapy than with phenol chemical peeling. This is attributed to the fact that pigmented epithelial

cells and melanocytes are more cryosensitive than other cell types. As early as one hour post-freezing, the melanocytes show swelling of mitochondria and nuclear damage. Tissue oedema is marked with pigment dispersed outside the cells, while adjacent keratinocytes are still unchanged[19]. Keratinocytes need to be frozen to -50°C for optimum destruction. Melanocytes are more delicate and only require a temperature of -5°C for destruction[20]. This fact is the reason for the resulting hypo-pigmentation following cryotherapy, with minimal changes in keratinocytes. Yet, the response to freezing injury varies from inflammatory to destructive, depending upon the severity of freezing. Minor freezing injury (short cryogen spurts) produces only inflammatory responses, while severe freezing injury (long cryogen spurts) destroys cells and tissues producing coagulation necrosis in the frozen tissue the days after thawing[21]. Thus, we recommend further studies with longer cryogen application periods that likely induce epidermal separation and re-epithelialization, with better clinical response.

In 1985, Kligman et al.[22] conducted long-term histologic follow up of phenol face peels. They demonstrated normal epidermal pattern in peeled skin, without cytologic irregularities, lentigos, and microscopic actinic keratoses. The basal keratinocytes contained many fine pigment granules rather evenly dispersed, with abundance of intermingled melanocytes. They concluded that the bleaching effect of phenol is not due to destruction of melanocytes, but due to impaired melanin synthesis, which is very long lasting (up to 20 years or even more). The long-lasting effect could be explained on basis of evidenced anti-proliferative activities of phenolic compounds against melanocytes[23]. On basis of the reported mechanisms of interference with melanin synthesis and deposition, phenols were categorized as peroxidase inhibitors, acting during active melanin synthesis[24]. The inhibition of peroxidase results in depigmentation or actually hypopigmentation by reduction of polymerization of melanogenic intermediates[25]. Therefore, phenol peeling bleaching effect results from melanopenia, melanocytopenia, and even dispersion of fine melanin in keratinocytes.

Since Melan-A immunostaining identifies melanocytes whether viable or not, electron microscopic examination was performed. We noticed that the melanocytes which escaped cryotherapy destructive effect contained small dark melanin granules with some aggregated complexes, and similarly did the keratinocytes. On the other hand, phenol-induced hypopigmentation was obviously due to impaired melanin synthesis, reflected as small dispersed melanin granules, mostly with light melanization. Follow up is recommended to investigate the long-lasting effect of phenol on melanin synthesis.

Conclusion

we realize that each of cryotherapy and phenol chemical peeling is effective in treatment of solar lentigines. However, Baker-Gordon phenol chemical peel showed better clinical response and higher patient's satisfaction, compared to 3-5 seconds of liquid nitrogen spray cryotherapy. Phenol chemical peeling better response is due to acting on both melanocytes and keratinocytes, normalizing their proliferative and melanization properties. However, by "cryo-peeling" comparable results could be achieved. Besides, more complications were reported with phenol peeling (greater pain intensity, prolonged healing time, and prolonged post treatment erythema). Nevertheless, resulting in better response or less complications is not the only parameter to choose a specific therapy for solar lentigines, as each modality of treatment is not recommended in the presence of certain medical condition. For example, phenol chemical peel is contraindicated in significant cardiac and renal diseases while cryotherapy is not recommended in case of cold intolerance and cold urticaria.

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