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Is There an Association Between Hyperbaric Oxygen Therapy and Improved Outcome of Deep Chemical Peeling? A Randomized Pilot Clinical Study

Y a-t-il un lien entre l'oxygénothérapie hyperbare et l'amélioration des résultats de l'exfoliation chimique? Un projet pilote clinique aléatoire

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Abstract

Background: Phenol chemical peeling (PCP) treatment is associated with prolonged recovery and sustained adverse events. Hyperbaric oxygen therapy (HBOT) is known to accelerate wound healing. The purpose of the current study was to evaluate the effect of HBOT on PCP recovery period and adverse events. **Methods:** This is a pilot randomized controlled clinical study. Women following PCP underwent 5 consecutive daily HBOT sessions, compared with PCP alone. Pain, pruritus, erythema, crusting, scaling, and edema were daily evaluated up to 28 days following PCP. Photographs taken on days 14 and 35 following PCP were assessed. Confidence to appear in public was assessed 14 days following PCP. **Results:** Eight participants equally assigned to HBOT and control groups. Lower severity scores for erythema, scaling, and pruritus were documented in the HBOT group (mean difference 1.19, $P = .006$; .84, $P = .04$; and 2.19, $P = .001$, respectively). Photographic assessment severity score was higher for skin tightness, edema, erythema, crusting, and scaling in the control group on day 14 post PCP ($P < .05$) and for erythema on day 35 post PCP ($P < .05$). Epithelialization percentage was higher in the HBOT group on day 14 post PCP compared with controls (98.5% $\pm$ 1% vs 94.2% $\pm$ 1%; $P = .021$). The HBOT group scored higher in confidence to appear in public (20.8 $\pm$ 1.7 vs 14.5 $\pm$ 1.3; $P = .029$). **Conclusion:** Hyperbaric oxygen therapy following PCP is associated with faster recovery as assessed by both patients and caregivers. So far, HBOT was mainly used in the treatment of problematic or chronic wounds. Our study suggests expanding the indications in which hyperbaric oxygen treatment is applicable and recommended.

Résumé

Historique : Le traitement par exfoliation chimique au phénol (ECP) s'associe à une convalescence prolongée et à des événements indésirables soutenus. On sait que l'oxygénothérapie hyperbare (OTHB) accélère la guérison des plaies. La présente étude vise à évaluer l'effet de l'OTHB sur la convalescence et les effets indésirables après une ECP. **Méthodologie :** Dans le cadre du présent projet pilote clinique aléatoire et contrôlé, des femmes ont suivi cinq séances d'OTHB quotidiennes consécutives auprès une ECP, par rapport à l'ECP seule. Les chercheurs ont évalué la douleur, le prurit, l'érythème, la formation de croûtes, la

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desquamation et l'œdème tous les jours jusqu'à 28 jours après l'ECP. Ils ont évalué les photos prises les jours 14 et 35 après l'ECP ainsi que la confiance à être vus en public 14 jours après l'ECP. **Résultats :** Huit participants participantes ont été réparties également entre l'OTHB et des groupes témoins. Le groupe d'OTHB présentait des scores de gravité plus faibles pour ce qui est de l'érythème, de la desquamation et du prurit (différence moyenne 1,19, $P = 0,006$; 0,84, $P = 0,04$; et 2,19; $P = 0,001$, respectivement). Le score de gravité par évaluation photographique était plus élevé pour ce qui est de l'élasticité de la peau, de l'œdème, de l'érythème, de la formation de croûtes et de la desquamation dans le groupe témoin le jour 14 après l'ECP ($P < 0,05$) et de l'érythème le jour 35 après l'ECP ($P < 0,05$). Le pourcentage d'épithélialisation était plus élevé dans le groupe d'OTHB le jour 14 après l'ECP que dans les groupes témoins (98,5 % $\pm$ 1 % par rapport à 94,2 % $\pm$ 1 %, $P = 0,021$). Le groupe d'OTHB a obtenu des scores de confiance plus élevés à être vus en public (20,8 $\pm$ 1,7 par rapport à 14,5 $\pm$ 1,3, $P = 0,029$). **Conclusion :** Selon l'évaluation des patientes et des soignants, l'OTHB s'associe à une convalescence plus rapide après l'ECP. Jusqu'à maintenant, l'OTHB était surtout utilisée pour traiter des plaies problématiques ou chroniques. D'après la présente étude, il est possible d'élargir les indications pour lesquelles l'OTHB est applicable et recommandée.

Keywords
chemical peels, clinical trials, dermatologic therapy, hyperbaric oxygen treatment

Introduction

Phenol is a deep chemical peeling (PCP) agent used for removal of fine and coarse facial wrinkling, irregular pigmentation localized to the dermis, and ablation of actinic keratosis.[1] It causes both keratolysis and keratocoagulation, followed by cutaneous regeneration that extends to the reticular dermis.[2-5]

Alongside its skin rejuvenation effect, PCP is associated with a prolonged recovery period and significant bleaching effect. Some of its adverse events include edema, pruritus and exfoliation of skin, photosensitivity, post peel hyperpigmentation, infection, milia, scarring, and long-standing erythema (up to 12 weeks).[5-7] Achieving a shorter recovery time with lower adverse events rate, especially erythema clearance, will allow a more tolerable and safer treatment.

Hyperbaric oxygen therapy (HBOT) augments tissue oxygen content and thus serves as a primary or adjunctive therapy for a diverse range of medical conditions such as decompression sickness, carbon monoxide poisoning, ischemia, aggressive soft tissue infections, non-healing ulcers, or compromised skin grafts and flaps.[8-13]

We hypothesize that HBOT would accelerate wound healing process and decrease the severity of local skin reactions. Therefore, the purpose of this study was to assess the effect of HBOT on adverse event rate and recovery time following PCP treatment.

Methods

Study Design

A pilot, open-label, randomized controlled clinical study was planned to assess the effect of HBOT on PCP outcome.

Ethical Approval

This clinical study was performed in accordance with the Declaration of Helsinki (1975) and was approved by the institutional review board. Prior to enrollment, participants were informed of the study procedures, possible risks, benefits, and complications. All participants signed an informed consent form. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Study Participants

We enrolled healthy, Fitzpatrick skin type 2, non-smoking women, aged 60 to 70 years old, who were candidates for PCP treatment. Participants who had a history of abnormal wound healing, keloid formation, autoimmune disease, or immunodeficiency and under immunosuppressive or systemic steroids or retinoid treatment were excluded. Participants were also excluded if they had received any facial chemical peeling or laser therapy up to 1 year prior to study occurrence.

Randomization

Following PCP treatment, each participant was randomly assigned to either HBOT or control group by opening a sealed envelope with its group allocation.

Hyperbaric Oxygen Therapy Protocol

The study group received 5 consecutive daily hyperbaric treatments, 1 hour long each, at 2 atm (202.65 kPa) with $F_{IO_2} = 1.0$ via face mask (held by patients who were instructed not to apply pressure), starting 7 days following PCP due to patient feasibility to attend the session.[14]

Phenol Chemical Peeling Protocol

All chemical peels were performed by a single dermatologist. Prior to treatment, skin type, hue, and indication for peeling were determined.

After each region of the face has been completely covered with the peeling solution (active ingredients phenol 65%, 0.6% croton oil), an occlusive dressing was applied for 24 hours. The occlusive dressing was removed at the next day and bismuth subgallate was

Table 1. Comparison of Participants' Self-Assessment 5-Point Mean Severity Score[a] Between HBOT (n = 4) and Control (n = 4) Groups.

Side Effect	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	*P* Valueb
Erythema									
HBOTc	5.0 (0.0)	4.3 (0.5)	3.5 (0.6)	2.8 (1.2)	2.3 (1.3)	2.0 (0.8)	1.5 (1.0)	1.3 (0.5)	.006
Control	5.0 (0.0)	4.8 (0.5)	4.3 (0.5)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	3.8 (0.5)	3.8 (0.5)	
Pain									
HBOT	3.3 (1.7)	3.0 (1.6)	2.3 (1.0)	1.8 (1.0)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	.75
Control	1.8 (1.5)	1.8 (1.5)	1.8 (1.5)	1.8 (1.5)	1.8 (1.5)	1.5 (1.0)	1.5 (1.0)	1.5 (1.0)	
Crusting									
HBOT	3.0 (1.4)	2.3 (1.3)	2.3 (1.3)	1.8 (1.0)	1.3 (0.5)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	.26
Control	3.5 (1.0)	3.3 (0.5)	2.8 (1.0)	2.8 (1.0)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	
Scaling									
HBOT	3.5 (1.0)	2.8 (1.0)	2.3 (0.5)	1.8 (0.5)	1.5 (0.6)	1.5 (1.0)	1.3 (0.5)	1.0 (0.0)	.04
Control	3.8 (0.5)	3.5 (0.6)	2.8 (0.5)	2.8 (0.5)	2.8 (0.5)	2.3 (0.5)	2.3 (0.5)	2.3 (0.5)	
Pruritus									
HBOT	2.5 (0.6)	2.5 (0.6)	1.8 (0.5)	1.5 (0.6)	1.8 (1.5)	1.8 (1.5)	1.3 (0.5)	1.0 (0.0)	.001
Control	4.5 (1.0)	4.0 (0.8)	3.8 (1.0)	4.0 (0.8)	4.5 (1.0)	3.8 (0.5)	3.5 (1.0)	3.5 (1.0)	

Abbreviation: HBOT, hyperbaric oxygen therapy treatment.
[a]Severity score for pruritus, pain, erythema, crusting, and scaling ranging from 1 (less severe) to 5 (more severe).
[b]*P* value was obtained using a repeated-measures test.
[c]Data presented as mean values (standard deviation).

applied to the facial skin for a week until reepithelizition. After a week, it was removed using Vaseline (day 7).

Follow-Up and Outcome

All PCP outcomes were assessed using a Likert scale 5-point severity score (5: severe, 4: moderately severe, 3: moderate, 2: mild, 1: none). Participants were asked to self-assess overall improvement of pain, pruritus, erythema, crusting, and scaling separately during days 7 to 14 following PCP.

Standardized digital facial photographs using identical camera (Nikon D60, Tokyo, Japan) and lightning settings were taken during a PCP follow-up examination on days 14 and 35. Photographs were used to assess participants' skin tightness, swelling/edema, erythema, crusting, and scaling by 2 independent investigators (a 20-year experienced dermatologist and a 10-year experienced plastic surgeon, both were unaware to patients' group ascription). All photographs were taken at afternoon hours.

Macroscopic quantification of the skin epithelialization was performed using the computer-assisted image analysis software NIS-Elements Ar (Nikon Instruments Europe BV, Amstelveen, the Netherlands), using a method described previously.[15] All participants filled a 5-item questionnaire on their confidence to appear in public, 14 days following PCP. Each item had a 5-point Likert scale. A summary score was used for analysis, ranges between 5 points (lowest confidence) and 25 points (highest confidence). Adverse events were assessed based on participant's self-report.

Data and Statistical Analysis

Statistical data were calculated by PASW, SPSS version 18 statistical software (IBM, Chicago, IL, USA). Continuous data are expressed as means (standard deviations). Daily patient scores were compared using repeated-measures test. Photographic assessments and public appearance confidence scores were compared using Mann-Whitney *U* test. Inter-observer agreement was assessed using Spearman ρ. The level of significance was defined as $P < .05$.

Results

A total of 8 participants who met the study criteria were enrolled to the study and randomly assigned to HBOT and control groups. Mean age was 62.9 ± 4.15 years in both groups ($P = .93$).

Participants Self-Assessment Comparison

No differences in mean severity scores between the HBOT and control groups for all categories were observed prior to HBOT (see Table 1, day 7 column). The mean severity scores of erythema and pruritus were lower in the HBOT group than in the control group (mean difference 1.23, $P = .015$ and 2.125, $P = .004$, respectively; see Table 1 and Figure 1).

Photograph Assessment

Photographic assessment mean severity scores of swelling, erythema, crusting, and scaling 14 days following PCP treatment were lower in the HBOT group ($P = .029$; see Table 2). Percentage of epithelialization at day 14 post PCP treatment was significantly higher in the HBOT group compared to controls ($98.5\% \pm 1\%$ vs $94.2\% \pm 1\%$; $P = .021$). Correlation coefficients of investigators' inter-observer agreement were 0.77 to 1 for all categories ($P < .05$). In Figures 2 and 3, photographs of representative cases from both the HBOT and control groups are shown.

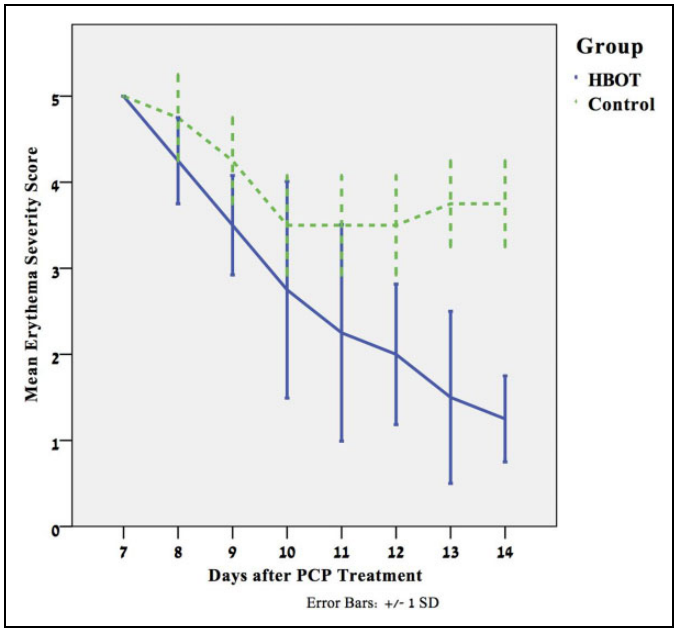

Figure 1. Comparison of participants' self-assessment 5-point mean erythema severity score between the HBOT (n = 4) and control (n = 4) groups. HBOT indicates hyperbaric oxygen therapy.

Appearance in Public Questionnaire

Confidence to appear in public questionnaire scored higher in the HBOT group than controls (20.8 ± 1.7 vs 14.5 ± 1.3, $P = .029$).

Adverse Event Report

No other systemic adverse event was reported by participants throughout the entire study and 3 months after the last follow-up examination.

Discussion

The goal of the pilot study was to assess whether HBOT can accelerate wound healing following PCP, as well as decrease the rate and severity of local adverse events and systemic complications. To our knowledge, this is the first study to demonstrate accelerated epithelialization rate and reduction in local adverse reactions following HBOT, as evaluated by both patients and caregivers. In addition, patients treated with HBOT felt more confident about public appearance sooner than controls. Finally, we found that HBOT was safe, well tolerated, and effective among study participants.

Table 2. Comparison of Photographic Assessment Mean Severity Scores[a] Between HBOT (n = 4) and Control (n = 4) Groups.

	Days Post Peeling					
	14			35		
Side Effect	HBOT[b]	Control	*P* Value[c,d]	HBOT	Control	*P* Value[d]
Tightness	1.88 (0.25)	4.75 (0.29)	.029	3 (0.41)	3.5 (0.58)	.343
Edema	1.88 (0.25)	4.75 (0.5)	.029	1.38 (0.48)	2 (0.41)	.114
Erythema	1.75 (0.29)	4.63 (0.48)	.029	1.5 (0.41)	2.75 (0.5)	.029
Crusting	1.63 (0.48)	4.13 (0.63)	.029	1.13 (0.25)	1.5 (0.58)	.486
Scaling	1.88 (0.25)	4.63 (0.48)	.029	1.13 (0.25)	2 (0.71)	.114
Epithelialization (%)	98.5 (1.0)	94.2 (1.0)	.021	100 (0)	100 (0)	NA

Abbreviations: HBOT, hyperbaric oxygen therapy treatment; NA, not applicable.
[b]Severity score for tightness, edema, erythema, crusting, and scaling ranging from 1 (less severe) to 5 (more severe). Epithelialization is presented as percentage of the treated skin area.
[c]Data are presented as mean values (standard deviation).
[d]*P* value was obtained using a Mann-Whitney *U* test.

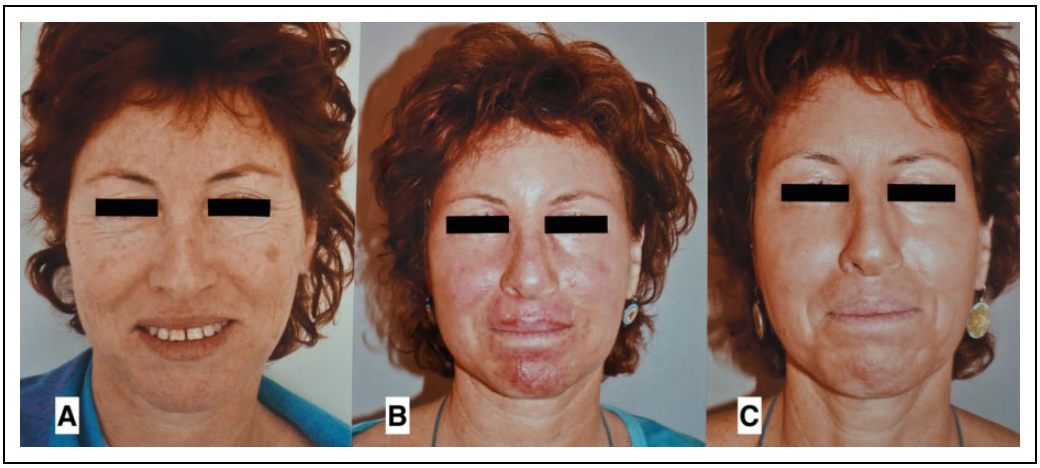

Figure 2. Photographic images of the control group participant (A) before PCP treatment, (B) 14 days after treatment, and (C) 35 days after PCP treatment. PCP indicates phenol chemical peeling.

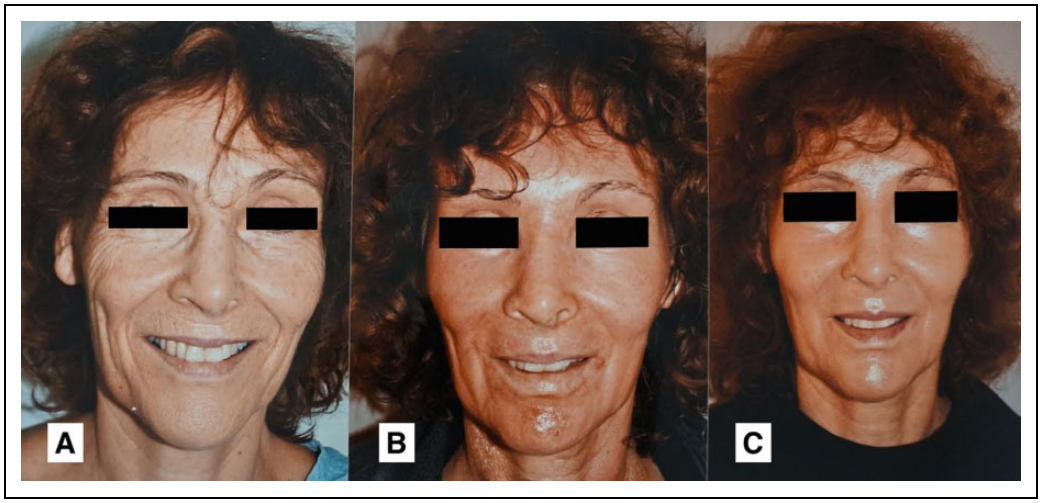

Figure 3. Photographic images of the HBOT group participant (A) before PCP treatment, (B) 14 days after treatment, and (C) 35 days after PCP treatment. HBOT indicates hyperbaric oxygen therapy; PCP, phenol chemical peeling

Hyperbaric oxygen therapy is known to accelerate wound healing through several physiological mechanisms. First, HBOT increases arterial oxygen partial pressure by 40 mm Hg or higher, thus allowing oxygen-dependent collagen matrix formation.[16] Another contribution to oxygen delivery to the wound site is achieved by stimulation of neovascularization by HBOT, either through increased oxygen gradient[17] or through triggering tumor necrosis factor α release.[18] In the cellular level, HBOT contributes to apoptosis attenuation and reduced inflammation through downregulating hypoxia-inducible factor-1α (HIF1α).[19] Increased tissue oxygenation is known to decrease peripheral edema and improve skin viability.[20] Up until now, HBOT was mainly used in the treatment of problematic or chronic wounds such as radiation necrosis and diabetic wounds. As for acute wounds, HBOT was mainly recommended for problematic acute wounds (eg, compromised flaps and grafts).[20] So far, HBOT effect on accelerated healing has been demonstrated in several human and animal studies.[21,22] In our study, we found increased epithelialization rates in the HBOT group. Together with decreased severity of adverse events following PCP treatment, and although they only received a single treatment about a week later, study results indicate the potential of HBOT to further accelerate wound healing in PCP treatment, if implemented earlier or even before the treatment and performed more than once.

Phenol chemical peeling is used for a variety of indications but is associated with prolonged adverse effects. To date, no clinical study was preformed to evaluate the benefits of HBOT on acute wounds such as those created by PCP. Attempts to minimize the side effects of phenol peel while maintaining its positive effects in previous studies were concentrated on developing various new phenol peeling formulas such as buffered phenol peel, Venner-Kellson, Baker Gordon, Litton, Mee, and Exoderm.[7] Another approach to minimize side effects was the use of different occlusive dressings and powders such as bismuth subgallate.[23]

In conclusion, this study innovates by showing that HBOT, in addition to its known benefits in problematic wounds, is also beneficial in accelerating the healing of the non-problematic wound and decreasing the side effects of facial peeling. Our study findings can also be relevant to other laser or chemically based skin resurfacing interventions, providing a faster recovery and milder skin inflammatory reactions compared to standard treatment.

Our pilot study was subject to several limitations such as small sample size not sufficient to assess accurate efficacy and less common adverse events of HBOT. In addition, study participants share a relatively narrow age span and the same Fitzpatrick skin type, and thus, we cannot apply our conclusions to other age and skin type groups.

Authors' Note

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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