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Topical treatment with oleocanthal extract in reducing inflammatory reactions after photodynamic therapy: a prospective quasi-experimental pilot study

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ABSTRACT

Objective: Photodynamic therapy (PDT) is an effective treatment against skin field cancerization. Its main side effect is local inflammation in the treated area. The phenolic compound oleocanthal (decarboxy methyl ligstroside aglycone), which is present in extra virgin olive oil (EVOO), has anti-inflammatory properties.

The purpose of this study was to evaluate the topical efficacy of an oily fluid enriched with oleocanthal (OC) extract, in comparison with a conventional oily fluid, in reducing the degree of inflammatory reaction after conventional PDT.

Methods: Quasi-experimental pilot study, before-after with a control group, performed with a cohort of consecutive patients diagnosed with actinic keratosis/field cancerization (AK/FC) in the forehead and/or scalp, treated by PDT. The study was carried out from April 2016 to November 2017 at a speciality hospital in southern Spain.

A group of 24 consecutive patients received the topical application, three times daily for one week, of an emollient oily fluid in the area treated with PDT. Subsequently, another group, of 23 consecutive patients, received the same treatment pattern with an oily fluid enriched with OC extract.

The post-PDT inflammatory reaction was measured by an independent member of the hospital's dermatology department, using the following visual scale of erythema (from 0 to 4).The assessment was conducted at 30 min and at 48 h post-PDT.

Results: In the assessment at 48 h after treatment, the inflammation had improved more among the patients treated with OC (median: 25%, 95%CI: -5.3 to 28.5) than in the non-OC group (median: 0%; 95%CI: -45.2 to -6.2). The difference was statistically significant ($p < 0.01$), and the Cohen's d value was 0.89 (large effect). At three months after PDT, a complete response had been obtained by 60.9% of the patients treated with OC compared to 29.2% of the non-OC group, and the difference was close to statistical significance ($p = 0.059$).

Conclusions: The topical application of an oily fluid enriched with OC extract achieved a greater reduction in post-PDT cutaneous inflammation and a better treatment response, in comparison with the application of a conventional oily fluid.

1. Introduction

Photodynamic therapy (PDT) is an effective treatment for actinic keratosis/field cancerization (AK/FC) and superficial non-melanoma skin cancer. Its main side effects are erythema and post-treatment oedema, and pain when exposed to light.[1] Severe post-PDT erythema is an uncomfortable and unpleasant consequence that heightens the possibility of subsequent retreatment being rejected and extends the duration of labour incapacity.[2]

Histamine, prostaglandin E2 (PGE2) and nitric oxide (NO) are all mediators of the cutaneous inflammatory response to PDT.[3,4]

The effectiveness of PDT in tumour destruction is thought to reside

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in three interacting mechanisms: the direct induction of apoptosis, damage to the vasculature associated with the tumour, and inflammation.[5]However, they may not coincide with the mechanisms that eliminate AK/FC, and the importance of inflammation following PDT has also been questioned.[2]In view of these considerations, it would be very useful to reduce the erythema induced by PDT after AK/FC treatment and, hence the time of post-treatment inactivity, if this can be done without jeopardising treatment efficacy.

Decarboxy methyl ligstroside aglycone, known as oleocanthal (OC), a phenolic compound present in extra virgin olive oil (EVOO), has a role as an antioxidant, neuroprotective, antineoplastic, apoptosis inducer and Hsp90 inhibitor agent.[6] Furthermore OC has anti-inflammatory properties similar to those of classical non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, which suppress the enzyme cyclooxygenase (COX), although not selectively.[7]

Taking into account that in vitro studies have shown that OC intervenes by inhibiting PGE2 (through the inhibition of COX) and nitric oxide synthase, we wished to examine whether the topical application of an EVOO fluid with OC extract might achieve a faster improvement from the acute inflammatory reaction provoked by PDT.

2. Methods

2.1. Study design and recruitment of patients

A quasi-experimental pilot study before-after with a control group was performed with a cohort of consecutive patients diagnosed with AK/FC in the scalp and/or forehead, and treated by conventional PDT irradiation with a red light lamp, using methylaminolevulinate cream as a photosensitiser. Two study branches were created. In the first group, the patients were given a topical application of an oily emollient fluid (composed by olea europeae, rosa moschata, amygdalus prunus dulcis, tocobiol c and matricaria recutita oil) on the PDT-treated skin. Those in the second group received the same type of oily fluid but enriched with OC extract. This was produced from extraction of high phenolic olive oil. The extract contained OC 50 %, oleacin 45 % and olive oil lipids 5 % (w/w). The levels were standardized using the nuclear magnetic resonance (NMR) spectroscopy published by Karkoula[8]. This extract was provided by the department of Pharmacognosy of the University of Athens.

In both groups, the treatment schedule was three times daily for one week. Epidemiological and clinical variables were recorded for all patients, at three time points: during visit 1 (immediately following the application of PDT), visit 2 (at 48 h after treatment) and visit 3 (at three months after treatment). The study was conducted from April 2016 to November 2017.

All patients were over 18 years of age, had previously agreed to participate in the study and had signed the corresponding informed consent form.

The exclusion criteria applied were dementia, coma or a state of confusion at the time of the study. Patients with a serious psychiatric history that would have prevented adequate follow-up were also excluded.

At the first visit, clinical and epidemiological variables (age, sex and relevant clinical history, such as hypertension or diabetes mellitus) were recorded, together with data concerning the treatment performed (surface area treated, in cm,[2]and previous PDT treatment for field cancerization).

The post-PDT inflammatory reaction was measured by an independent member of the hospital's dermatology department, using a visual scale of erythema (VSE) with five grades: 0 (without erythema), 1 (minimal erythema, hardly noticeable), 2 (moderate erythema, pink skin), 3 (more intense erythema, dark pink/red skin), 4 (broken, eroded skin). The assessment was conducted at 30 min and at 48 h post-PDT.

Pain was assessed using a visual analogue scale (VAS), scored from 0 to 10 (0 = no pain, 10 = worst imaginable pain) in the treated area, immediately after the procedure and at 48 h.

The presence of exudative/scabbed lesions and of infection (the latter, if suspected, was confirmed by culture) was determined at the second visit (at 48 h after PDT).

The response to PDT treatment was evaluated at three months,

Table 1
Sociodemographic data, clinical characteristics and results obtained for the study population, segmented by treatment group.

	No OC		OC		P
	n	%	n	%	
Sex					
Man	24	100	20	87	0.109
Woman	0	0	3	13	
Age					
Median - IQR	*72.5*	*69.2 - 81.7*	*72*	*69 - 80*	0.881
Hypertension					
No	13	54.2	14	60.9	0.865
Yes	11	45.8	9	39.1	
Diabetes Mellitus					
No	20	83.3	22	95.7	0.348
Yes	4	16.7	1	4.3	
Treatment area (cm^2)					
Median - IQR	*159*	*105 - 200*	*132*	*100 - 198*	0.166
Previous photodynamic therapy					
No	15	62.5	19	82.6	0.225
Yes	9	37.5	4	17.4	
Pain (VAS 48 h)					
Median - IQR	*2*	*0.5 - 2*	*2*	*1 - 2*	0.962
Erosions-Crusts					
No	11	45.8	16	69.6	0.177
Yes	13	54.2	7	30.4	
Signs of infection					
No	22	91.7	22	95.7	1.0
Yes	2	8.3	1	4.3	
Difference Relative % - Inflammation change (Basal-48 h)					
Median - IQR	*0*	*-50 - 0*	*25*	*0 - 33*	0.002
Response to treatment (3 months)					
No response - Partial	17	70.8	9	39.1	0.059
Complete	7	29.2	14	60.9	

Data were analyzed using the Mann-Whitney U test for quantitative variables and the chi-square test (or Fisher's exact test when the expected frequencies were < 5) for qualitative variables. IQR: Interquartile range. No OC: group without oleocanthal. OC: group with oleocanthal.

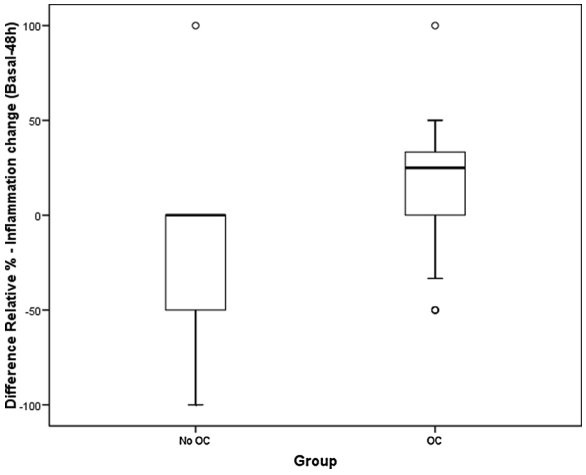

Fig. 1. Box-plot of the relative percentage distribution of inflammation change (Baseline – After 48 h)/ No OC: group without oleocanthal. OC: group with oleocanthal.

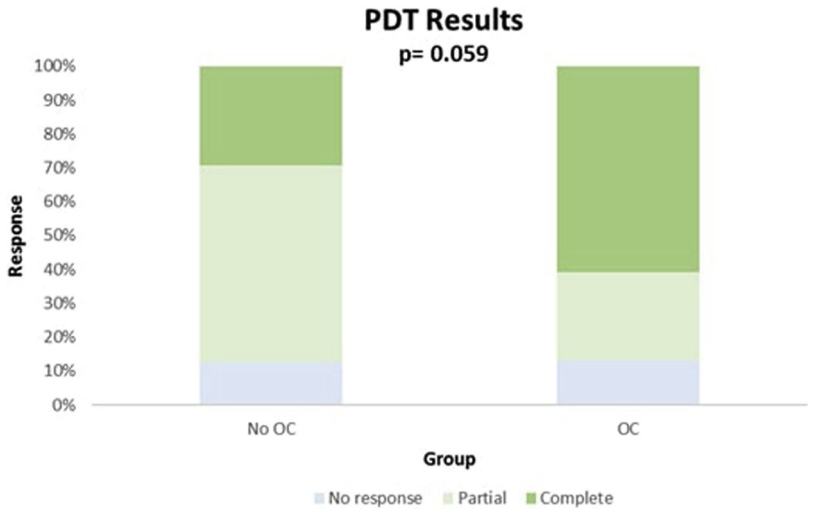

Fig. 2. Bar chart of the distribution of clinical responses at three months after starting PDT treatment/ p-value corresponding to chi-square test.

according to a three-level classification: no response, partial response or complete response.

The study was approved by the Costa del Sol Hospital Research Ethics Committee, under code number 02_16_Oleocantal_TFD. The product used in the project is a natural compound, the active ingredients of which are 100% plant-derived, which is registered in the Cosmetic Products Notification Portal.

2.2. Statistical analysis

The descriptive analysis performed was segmented by treatment group, determining the median and interquartile range (IQR) for quantitative variables and the frequency distribution for qualitative variables. The treatment groups were compared using the Mann-Whitney U test for quantitative variables and the chi-square test (or Fisher's exact test when the expected frequencies were < 5) for qualitative variables. The level of statistical significance was taken as $p < 0.05$ for the one-tailed tests. All analyses were performed using SPSS statistical software, version 16.0 (SPSS Inc).

3. Results

Following PDT, 24 patients were treated consecutively with an oily fluid without OC, and another 23, consecutively with a similar fluid containing OC. There was no treatment dropout in either of the groups. Overall, the patients in the study sample had an average age of 73.1 (SD: 9.2) years, and 93.6% were male. There were no differences in the distribution of variables such as hypertension, diabetes and average surface area between the two treatment groups. At baseline, the group without OC had a median VSE score of 2 (IQR: 2-2), versus a median score of 3 (IQR: 2-3) in the patients treated with OC (Table 1).

In the assessment at 48 h after treatment, the post-PDT inflammation was more sharply reduced in the group of patients treated with OC (median: 25%, 95%CI: -5.3 to 28.5) than in those without OC (median: 0%, 95%CI: -45.2 to -6.2). These differences were statistically significant ($p < 0.01$), for a Cohen's d of 0.89 (large effect) (Fig. 1).

At 48 h after treatment, the degree of pain reported, among both groups, had a median value of 2. The presence of erosions-scabs was reported by 54.2% of the patients without OC, compared to 30.4% of those in the OC group, although the difference was not statistically significant ($p = 0.177$). Regarding the PDT results at three months, 60.9% of the patients with OC achieved complete response, compared to 29.2% of those without OC, and the p value was close to significance (0.059) (Fig. 2).

4. Discussion

OC is a phenolic compound that is present in some EVOO and has important anti-inflammatory properties. It is believed to be responsible for the sensation of itching in the throat when certain EVOOs are swallowed and to inhibit the activity of the enzymes COX-1 and COX-2.[7,9]The inhibition of these enzymes is a fundamental aspect of the anti-inflammatory action of ibuprofen and other NSAIDs, and so OC can advantageously be used to alleviate both inflammation and pain. OC exhibited dose-dependent inhibition of the enzymes COX-1 and COX-2 in vitro, and was more potent in inhibiting these inflammatory enzymes at equimolar concentrations in comparison to ibuprofen.[9–11]Beauchamp et al also reported that 25 mM OC inhibited 41–57% of COX activity in comparison to 25 mM ibuprofen, which inhibited 13–18% COX activity in vitro.[9] Furthermore, it has been reported that compounds with OC penetrate the stratum corneum more easily than those based on traditional NSAIDs. OC can be used in diverse forms, such as gels, lotions, suspensions, creams, aerosols or transdermal patches.[12]

In vitro studies have shown that OC inhibits PGE2 (via the inhibition of COX) and nitric oxide synthase,[11,13] and therefore an EVOO cream with OC extract could be applied to quickly reduce an acute inflammatory reaction to PDT.

It has also been reported that PDT itself induces the release of COX-2, thus promoting the regrowth of cancer cells.[14]Consequently, the application of an OC-rich oily fluid could be considered in future studies as an adjuvant treatment to slow or halt such regrowth.

Following its discovery and identification, OC has been reported to present various modes of action in alleviating diseases associated with inflammation, including degenerative joint disease, neurodegenerative disease and even specific cancers.[7,11,15–18]

Specifically in dermatology several studies have reported different ways in which OC induces apoptosis and inhibits the migration, angiogenesis and metastasis of cancerous cell lines originating from melanoma and non-melanoma skin cancer.[18–20] Polini et al discovered that EVOO extracts reduced non-melanoma skin cancer cell viability and migration, prevented colony and spheroid formation, and inhibited proliferation of atypical keratinocytes stimulated with epidermal growth factor. Such a pharmacological activity was promoted by OC and oleacein through the inhibition of Erk and Akt phosphorylation and the suppression of B-Raf expression.[19]Also these same authors showed in vitro studies that OC induced cytotoxicity in melanoma cells without effect on normal cells.[20]In this way, further studies are required to assess the antitumor capacity of OC under conditions of real-life use.

5. Conclusions

The topical application of an oily fluid containing OC extract achieves a greater reduction in post-PDT cutaneous inflammation and a better therapeutic response than the application of a conventional oily fluid without OC. The present study is the first to consider the applicability of this phenolic compound, contained in EVOO, in dermatological treatment.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2018.12.003.

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