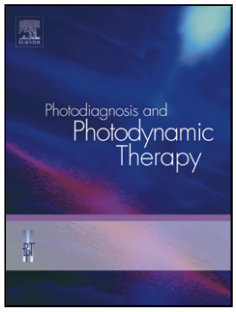

Efficacy of lidocaine 7%, tetracaine 7% self-occlusive cream in reducing MAL-cPDT-associated pain in subjects with actinic keratosis: A randomized, single-blind, vehicle-controlled trial (The "3P-Trial")

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Efficacy of lidocaine 7%, tetracaine 7% self-occlusive cream in reducing MAL-cPDT-associated pain in subjects with actinic keratosis: A randomized, single-blind, vehicle-controlled trial (The "3P-Trial").

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Highlight

- Conventional photodynamic therapy (cPDT) is considered a very effective treatment of actinic keratosis (AK) lesions. However, its use is limited by the fact that this procedure could be very painful.
- A self-occlusive topical 7% lidocaine/7% tetracaine anesthetic cream (LT-C) approved by the FDA to provide local topical anesthesia in adults undergoing superficial dermatological procedures is available.
- There are no data regarding its pain reducing effect during cPDT. We perform a prospective, randomized, single-blind, two-center trial (The 3P-Trial) to assess the pain reduction effect of LT-C versus vehicle cream in subjects with AK undergoing cPDT.
- We perform a prospective, randomized, single-blind, two-center trial to assess the pain reduction effect of LT-C versus vehicle cream in subjects with AK undergoing cPDT.
- Fifthy AK subjects with on average 17 lesions were enrolled in the 3P-trial.
- In the group treated with active cream the VAS score was reduced by -47% in comparison with the control group (P=0.0009),
- The 3P-trial has demonstrated that the preventive application of the self-occlusive lidocaine 7%-tetracaine 7% cream is very effective in reducing the procedure-associated pain during MAL-cPDT for the treatment of AK lesions.

Abstract

Introduction

Conventional photodynamic therapy (cPDT) is considered a very effective treatment of actinic keratosis (AK) lesions. However, its use is limited by the fact that this procedure could be very painful. The use of topical anesthetics such as tetracaine or lignocaine/prilocaine has shown disappointing results in term of pain reduction. A self-occlusive topical 7% lidocaine/7% tetracaine anesthetic cream (LT-C) approved by the FDA to provide local topical anesthesia in adults undergoing superficial dermatological procedures is available. There are no data regarding its pain reducing effect during cPDT. We perform a prospective, randomized, single-blind, two-center trial (***The 3P-Trial***) to assess the pain reduction effect of LT-C versus vehicle in subjects with AK undergoing cPDT.

Material and Methods

Fifty AK subjects (74±10 years, 32 men, 18 women) with on average 17 lesions were enrolled after their written informed consent. Eight subjects presented also a total of 16 basal cell carcinoma lesions. Twenty-five were randomized to LT-cream, applied 1 hour before the Methyl amino levulinate (MAL)-cPDT session and 25 to cream vehicle. The main outcome was the patient-assessed evaluation of pain score during and just after the conclusion of cPDT session (mean of the two values) using a 10-point visual analog scale (VAS). The cPDT session (LED Red light 630 nm) was performed with a duration of 6±2 min with a standard fluence of 37 J/cm2. All treated lesions were prepared by gentle superficial curettage.

Results

All the randomized subjects concluded the trial. The mean±SD of VAS score in vehicle group was 6.2±2.7 (95% CI of the mean: 5.0-7.5). In the group treated with LT-cream the VAS score was 3.3±1.9 (95% CI of the mean: 2.5-4.1). The active cream reduced the VAS score by 47%. Median values of pain VAS score in the active group was reduced by 60% in comparison with vehicle group (3.0 vs 7.5). The difference between the two groups was statistically significant (p=0.0009; Mann-Whitney test).

Discussion

The 3P-trial has demonstrated that the preventive application of the self-occlusive lidocaine 7%-tetracaine 7% cream is very effective in reducing the procedure-associated pain during MAL-cPDT for the treatment of AK lesions.

Key Words: Actinic Keratosis, Photo-dynamic Therapy, Lidocaine, Tetracaine, Randomized trial

Introduction

Conventional photodynamic therapy (cPDT) is a very effective treatment modality of actinic keratosis (AK) lesions[1]. This procedure is also effective in the treatment of other skin cancers, like basal cell carcinoma and squamous cell carcinoma, in their early stage[2]. However, its use is limited by the fact that this procedure could be very painful[3]. In fact, pain is a significant drawback of cPDT, especially when large area should be treated[4]. In some cases, during cPDT sessions, patients experience such severe pain that the light session should be stopped[5]. The use of topical anesthetics such as tetracaine[6] or lignocaine/prilocaine[7] has shown disappointing results in term of pain reduction in comparison with no treatment in this clinical setting. Effective anesthetic procedures seem to be nerve block[8], subcutaneous infiltration anesthesia[9] and transcutaneous electrical nerve stimulation[10]. However, these procedures could be not easy to handle, and their safety profile could be sub-optimal. Cold analgesia is commonly used but the efficacy is limited[11]. A self-occlusive topical 7% lidocaine/7% tetracaine anesthetic cream (LT-C) approved by the FDA to provide local topical anesthesia in adults undergoing superficial dermatological procedures is available[12]. This cream can reduce dermatological procedure-associated pain by -41% in comparison with vehicle[13]. There are no data so far regarding its pain reducing effect during cPDT.

Study Aim

To assess the procedure-associated pain reduction effect of LT-C versus cream vehicle in subjects with AK undergoing cPDT.

Study Design

This was a non-sponsored, prospective, randomized, balanced (1:1), parallel-group, single-blind two-center trial (The "3P-Trial") conducted in Italy.

Material and Methods

a) Subjects

Subjects aged 18 years or older with a clinical and dermoscopy diagnosis of multiple AK lesions of the face or scalp were eligible for the trial. Exclusion criteria were all the clinical

conditions with a clear contraindication to PDT. Fifty AK subjects (74±10 years, 32 men, 18 women) with on average 17 lesions were enrolled after their written informed consent. The study was conducted between November 2019 and January 2020. Enrolled patients were affected by multiple AK lesions (a total of 834 lesions). Eight subjects presented also a total of 16 basal cell carcinoma lesions. The average number of AK lesions per treatment side (field cancerization) was 9 in both groups. Twenty-five were randomized to LT-cream, applied for 1 hour before the Methyl amino levulinate (MAL)-cPDT session and 25 to cream vehicle. A total of 235 AK lesions were treated in the active group and 230 AK lesions in the control group. Both the products were removed just before MAL application. Randomization procedure was performed using a computer-generate allocation treatments list. In more details, randomization was done by generating a consecutive numbers list (from 1 to 60 with a block of 4) and then allocating these numbers to active or control. The vehicle was a simple emollient cream without any anesthetic active compound. Patients were unaware of the differences between the active cream and the control cream. The list of numbers was kept safely and was not accessed until study completion.

b) Main Outcome

The main outcome was the patient-assessed evaluation of pain score during and just after the conclusion of cPDT session (mean of the two values) using a 10-point visual analog scale (VAS 0-10 scale)[14]. Pain was assessed by the patient putting a mark in the 10-point scale from 0 (no pain at all) to 10 "worst pain ever". The investigator recorded the numerical pain score and the subject was not aware of this value.

c)cPDT Session

The cPDT session (LED Red light 630 nm; Aktilite lamp; Photocure ASA, Oslo, Norway) was performed with a duration of 6±2 min and with a standard fluence of 37 J/cm2. All treated lesions were prepared by gentle superficial curettage. Before irradiation, MAL 16% cream was applied as 1-mm thick layer under occlusion for 3 hours.

d)Ethical aspects.

The study protocol was approved by the local Institutional Review Board in October 2019 and was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki[15]. All the participating subjects gave written informed consent to participate.

e) Statistical Analysis and Sample size

Statistical analysis was performed using GraphPad statistical software ver. 13.0 (La Jolla, CA, USA). Continuous variables were expressed as mean±Standard Deviation (SD). Analysis was based on the Intention-to-treat principle with all subjects included in their assigned treatment group. The primary endpoint of the trial was the mean VAS score value. The Mann-Whitney test was used for the analysis of the study outcome (comparison between the two groups). We calculated also the 95% Confidence intervals of the difference in all the variables evaluated. This was a superiority trial. In a study comparing daylight PDT with conventional PDT, Fargnoli et al[16]. found that the VAS average score value in cPDT treated patients was 4.4±1. We hypothesized that VAS score mean values in the active group would be lower in comparison with the control by at least -35%. This reduction was in line with the results of several studies evaluating the efficacy of this anesthetic cream in comparison with the vehicle[17]. Therefore, sample size evaluation was performed calculating the hypothetical absolute difference in VAS score mean values between the two groups of 2.4 points in a 10-point VAS scale (from 4.4±1 to 2.8±1). With an effect size (Cohen's d value) of 0.4, with an alpha value of 0.05 and a power of 90% a total of at least 50 subjects should be enrolled to detect this difference. The sample size was calculated using G-Power statistical software version 3.9 (Kiel, Germany). A p-value of <0.05 was considered as significant.

Results

All the randomized subjects concluded the trial. AK lesions were located on the scalp (55%) and on the face (45%). Groups demographic characteristics at baseline are detailed in Table 1. Figure 1 shows the study flow. The two groups were well balanced regarding

the variables evaluated and recorded. The mean±SD of VAS score in vehicle group was 6.2±2.7 (95% CI of the mean: 5.0-7.5) with a median value of 7.5. In the group treated with LT-cream the VAS score was 3.3±1.9 (95% CI of the mean: 2.5-4.1) with a median value of 3.0. The active cream reduced the mean VAS score by 47% with an absolute difference of -2.9 points (95% CI of the mean difference: from -4.4 to -1.1) (Figure 2). The difference between the two groups was statistically significant (p=0.0009; Mann-Whitney test). VAS scores median values in subjects treated with the active cream in comparison to vehicle group were reduced by 60% (3.0 vs. 7.5). In two subjects (one per group) the cPDT session was stopped prematurely after 3 min due to excessive pain (with a VAS score of 8 and 9, respectively). No severe side effects were reported.

Discussion

Conventional PDT is a very effective treatment of AK and others skin cancers at the early stage[18]. Conventional PDT is considered the standard treatment procedure to control field cancerization[19]. The pain associated with cPDT limits the widespread use of this procedure[20]. In some cases, the pain could cause the early termination of treatment session with a consequent decrease of the overall therapeutic efficacy. Pain associated with PDT could be influenced by several factors like the photosensitizer molecule used[21] (ALA is in general more painful than MAL), by the procedure[22] (daylight PDT is less painful or practically pain-free in comparison with cPDT) and by irradiance level[23]. Several interventions on PDT-associated pain have been attempted and evaluated. Nerve block, subcutaneous infiltration anesthesia, cold analgesia and transcutaneous nerve stimulation seem associated with less PDT-associated pain in comparison with no treatment[8-11]. On the contrary, topical anesthetic gels have demonstrated limited efficacy in reducing pain[24]. However, the latter could be a more convenient and safe procedure in comparison with the former. So far, there is not a validated protocol for the PDT-related pain management. The self-occlusive topical 7% lidocaine/7% tetracaine anesthetic cream (LT-C) has shown to be a potent pain-killing strategy in several dermatological procedures like laser-assisted tattoo and hair removal[25]. In the present trial, in comparison with vehicle, this cream has reduced the mean VAS score by 47% on average. The reduction in median values was

60%. The absolute difference in VAS score mean values we have observed in this study (-2.9 cm) suggests that this anesthetic cream could be more effective than cold analgesia (-1.0 point)[11,26] but less potent than nerve block (-4.2 points)[8]. However, lacking "head-to-head" comparative trials it is so far impossible to identify which strategy could be better. Published trials have shown that morphine gel, tetracaine gel and eutectic mixture of lidocaine 2.5% and prilocaine 2.5% were not able to reduce pain during cPDT in comparison with placebo[6-7,23]. The product we have evaluate in this trial is a self-occlusive eutectic mixture of lidocaine 7% and tetracaine 7%. The anesthetic effect of this cream is reliable and long-lasting: up to 9.4hrs in clinical studies[27]. This latter aspect makes this product an ideal pain-reducing approach in cPDT because it is possible to apply the product just 60-30 minutes before the application of the photosensitizer (in our case MAL) which should stay for at least 3 hours before performing the cPDT session. This anesthetic cream applied before starting cPDT could be also useful to reduce the pain related to the de-bulking procedures for keratin excess removal in case of hyperkeratotic AK lesions. So far, no data regarding the efficacy of this anesthetic cream in reducing PDT associated pain have been available. Our study demonstrated for the first time that this anesthetic cream is active in reducing procedure-related pain in subjects treated with cPDT for AK or early skin cancers. Some study limitation should be taken in account in interpreting our results. First the study was performed in a relatively small group (50 subjects). However, we have performed an accurate sample size calculation which has identified in this number the adequate sample size group. The second aspect was related to the study design, the present trial was a randomized, single blind study; not a double blind. However, the main outcome of the trial was strictly related to the patient's evaluation, unaware of the type of treatment (active vs. cream vehicle). Another critical point was that we evaluated the pain during and just after the conclusion of the PDT. Therefore, we do not have data regarding the duration of anesthetic effect several hours after the procedure.

Conclusion

The 3P-trial has demonstrated that the preventive application of the self-occlusive lidocaine 7%-tetracaine 7% cream is very effective in reducing the procedure-associated pain during MAL-cPDT for the treatment of AK lesions.

Acknowledgments and Authors' Contribution

This was a non-sponsored trial. MBB and MP defined the study protocol and performed all the clinical evaluations and the cPDT procedures. They were also involved in data collection and analysis. MM is an employee of Cantabria Labs Difa Cooper, the Company which sells the anesthetic cream. MM was exclusively involved in the preparation of the final version of the manuscript.

Table I

	Active cream group	Vehicle Group
Subjects (men/women)	25 (17/8)	25 (15/10)
Mean age, years	73±11	75±9
Fitzpatrick Photo type (n, %)		
I	2 (8%)	3 (12%
II	11 (44%)	12 (48%)
III	12 (48%)	10 (40%)
Total number of AK lesions	425	409
Distribution		
Scalp	54%	55%
face	46%	45%
AK Type		
AK I	82%	81%
AK II	14%	15%
AK III	4%	4%
Average Number of AK lesions per treatment site	9.4	9.2
Duration of cPDT session, (min, sec)	6 min 35sec	6 min 28 sec

Figure 1

Study's Flow diagram

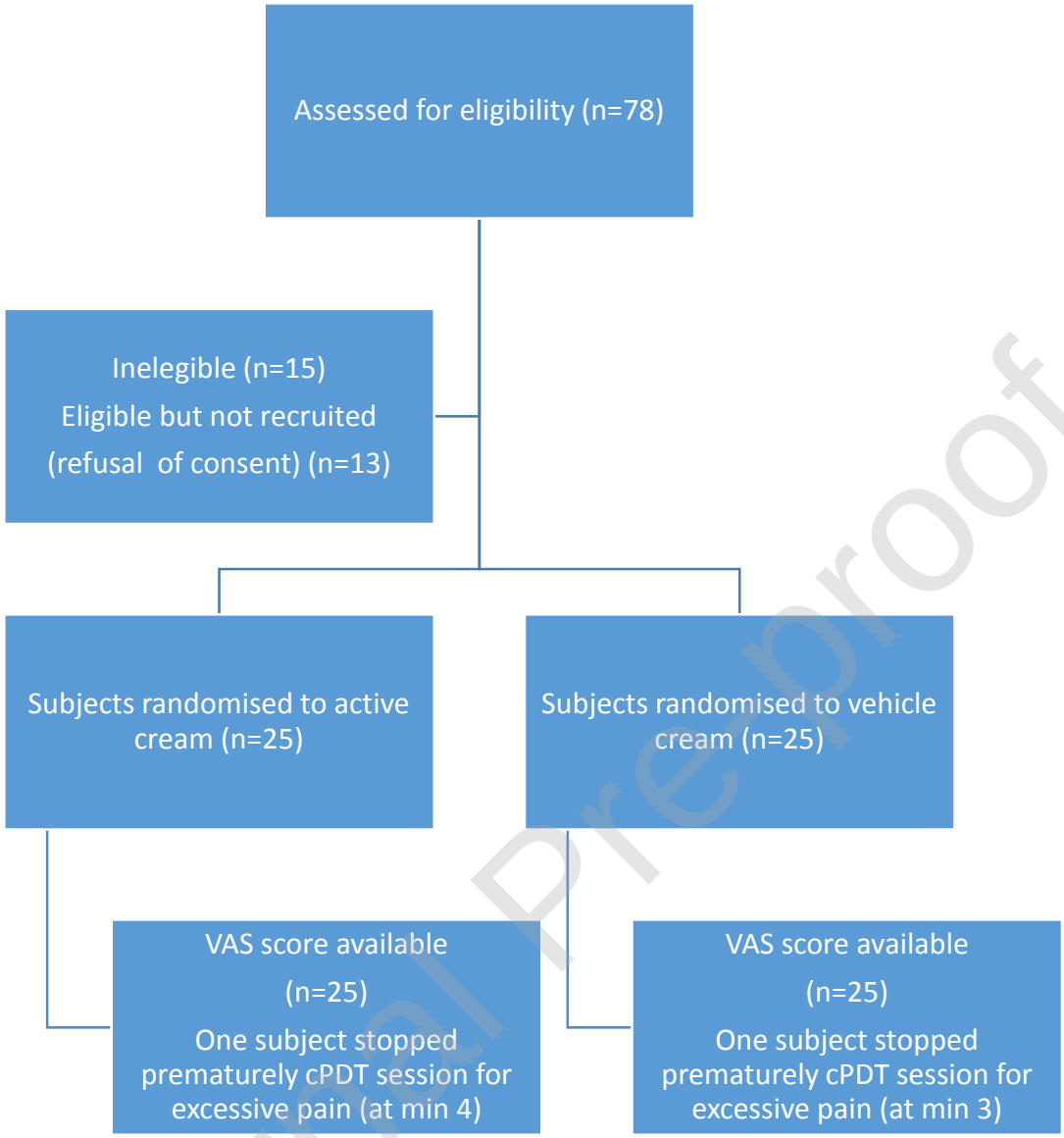
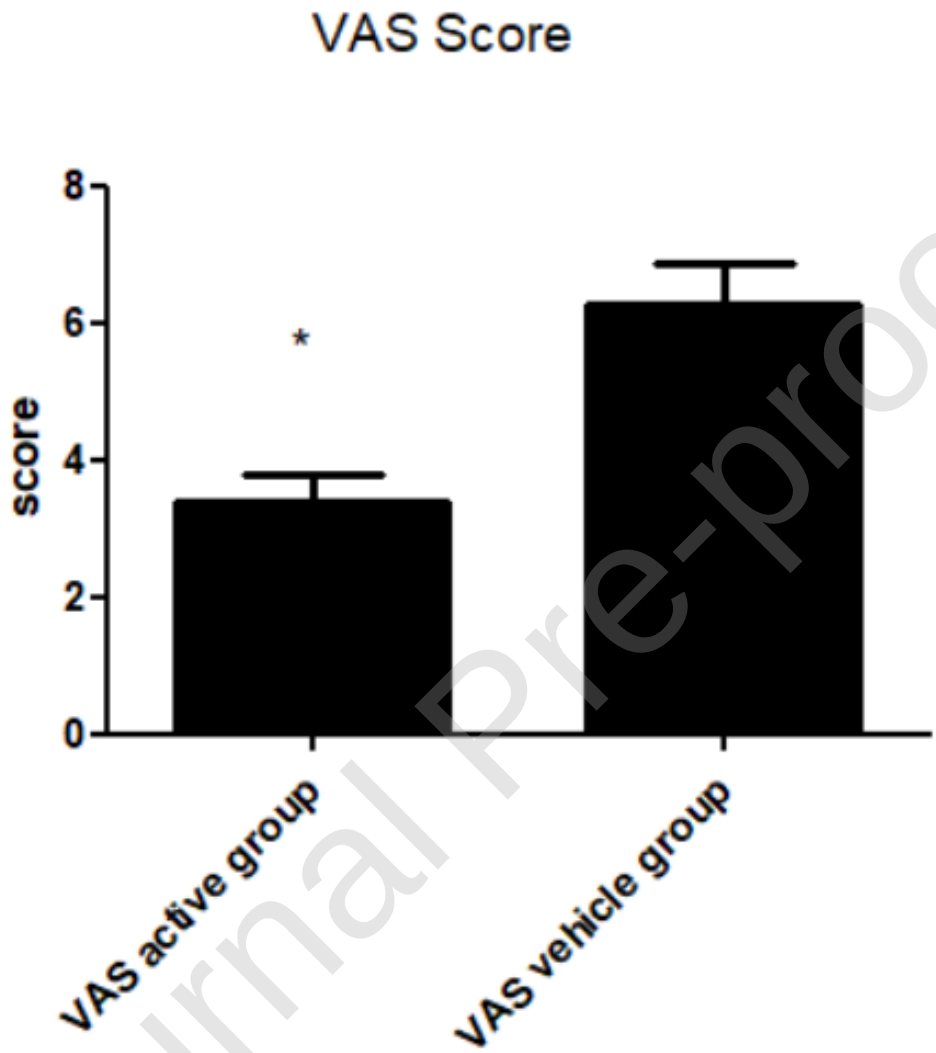


Figure 2

Average (±SD) VAS pain score (scale from 0 to 10) in the two groups.

=P0.0009; Man Whitney Test.



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