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Pain reduction in patients after applying a nitrous oxide/oxygen mixture (Livopan) during photodynamic therapy: study protocol for an observational study (Livopan study)

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ABSTRACT

Introduction: Photodynamic therapy (PDT) is an effective treatment option for extensively photodamaged skin with multiple actinic kerastosis. However, the main drawback of PDT is the intensive pain experienced during its application, which makes it frequently necessary to interrupt or even terminate the process resulting in incomplete treatment. Several strategies for controlling pain during PDT have been studied but few effective methods are currently available. Alternative options are urgently needed. Livopan, a nitrous oxide/oxygen mixture, is indicated for the treatment of short-term pain conditions when rapid analgesic onset and offset effects are wanted. But so far, there are no studies evaluating the effect of Livopan on pain intensity during PDT. Therefore, it remains unclear whether patients benefit from this inhalation analgesia. Within the Livopan study, this issue will be evaluated for the first time.

Methods and analysis: The Livopan study is a prospective, single-centre, explorative, controlled, observational study to investigate the pain reduction in patients after applying a nitrous oxide/oxygen mixture (Livopan) during PDT according to the visual analogue scale in 60 patients.

Ethics and dissemination: Ethics approval was provided by the ethics committee of the medical faculty of the University of Heidelberg. Ethics approval number S-169/2014.

Trial registration number: German Clinical Trial Register (DRKS): DRKS00006054.

Strengths and limitations of this study

- For the first time, the effect of Livopan on pain intensity during photodynamic therapy will be evaluated.
- This is a non-commercial study.
- The Livopan study is designed as an observational study but randomised controlled trials generate the most reliable evidence of intervention efficacy. Nevertheless, the protocol described here is a necessary preliminary step in this challenging area of research where there are no effective interventions available. If successful, this observational study will assist to implement randomised controlled trials.

INTRODUCTION

Background/rationale

Non-melanoma skin cancer, including actinic keratosis (AK), is the most common malignancy in the Caucasian population. AK is an early in situ squamous cell carcinoma and untreated lesions have up to 20% risk of progression into an invasive squamous cell carcinoma, which has metastatic potential.[1] In patients with multiple AK, so-called 'field cancerisation', topical photodynamic therapy (PDT) is highly effective with an excellent cosmetic outcome. The procedure can be used over large areas in a single treatment session. However, the main drawback of PDT is the pain experienced during its application. It often manifests as a burning, stinging or prickling sensation, and usually peaks in the first minutes of treatment and declines significantly after 8 h.[2] It is usually intense and in some cases even intolerable for patients, sometimes requiring the interruption or termination of the process resulting in incomplete treatment. Kasche *et al*[3] found that 54% of patients treated with aminolevulinic acid discontinued treatment because of unbearable pain. Several strategies for controlling pain during PDT have been studied. Although some of them achieve a reduction in levels of pain, none were completely effective. Alternative options are needed to reduce pain during PDT. Livopan, a nitrous oxide/oxygen mixture, is indicated for the treatment of short-term pain conditions of mild-to-moderate intensity when rapid analgesic onset and offset effects are wanted.

Anxiolysis, easy self-administration, fast onset and complete recovery after a few minutes, and the low ratio of side effects, make the Livopan inhalation an ideal addendum in pain management. Consequently, dermatologists, paediatrics, gynaecologists and dentists increasingly use Livopan.[4 5] But, to date, there are no studies evaluating the effect of Livopan on pain intensity during PDT. Therefore, it remains unclear whether patients benefit from this procedure.[6] The aim of the Livopan study is to observe the pain reduction in patients after applying Livopan during PDT according to the visual analogue scale (VAS), and to observe the time of the first interruption (seconds) and the number of interruptions due to pain during illumination.[7] Additionally, treatment satisfaction is scored immediately after treatment using the German version of the Treatment Satisfaction Questionnaire for Medication (TSQM).[8]

Objectives

The objectives of this study are to observe the pain reduction in patients after applying Livopan during PDT according to the VAS, and to observe the time of the first interruption (seconds) and the number of interruptions due to pain during illumination. Additionally, treatment satisfaction is scored immediately after treatment using the German version of the TSQM.

DESIGN/METHODS

Study design

The Livopan study is designed as a prospective, single-centre, explorative, controlled, observational study.

Recruitment and status of the study

Approval of the ethics committee was granted on 28 July 2014. The date of first enrolment was 1 August 2014. The recruitment of patients is in progress. The estimated total time frame for recruitment of 60 patients is 6 months. The total duration of the study is expected to be 9 months, including analysis.

Study population

Sixty patients with multiple AK of both cheeks receiving an extensive treatment of the complete photodamaged area in our dermatological outpatient department will be observed.

Criteria for inclusion/exclusion

Patients scheduled for PDT of both cheeks at the Department of Dermatology, University of Heidelberg, Germany, equal to or greater than 18 years of age, who have given written informed consent, will be eligible. Patients with impaired mental state, patients deemed to have insufficient understanding of the German language will be excluded from the Livopan study.

Methods

Preparation for illumination with red light starts with a gentle curettage of the affected area. Then the photosensitiser, Metvix (Galderma-Spirig, Egerkingen, Switzerland), is applied on the entire field, covered with occlusive dressing and protected from light by aluminium foil and adhesive bandage. After an incubation of 3 h the bandage is removed and the photosensitiser gently wiped off. The irradiation is performed using a red light-emitting diode lamp (Aktilite, Galderma, Lausanne, Switzerland) with a peak emission of 630 nm using a total light dose of 37 J/cm^2. Patients are offered short interruptions from illumination if necessary. All patients receive oral analgesics with 800 mg ibuprofen 30 min before irradiation. Furthermore, during the procedure, the treated area is cooled with a cold air fan (CRIOjet Air C50, Linde Gas Therapeutics GmbH, Niefern-Öschelbronn, Germany). The PDT starts with irradiation of one cheek.

For our study, patients experiencing severe pain of VAS ≥6 during PDT of one cheek, in spite of oral and cold air analgesia, will be offered additional Livopan analgesia for PDT of the contralateral side of the face. Livopan will be administered after a critical review of potential contraindications. Recruitment of patients will be performed until 30 patients per group are included. The assumption that the number of patients per group will be balanced seems to be reasonable from our daily practical experience. However, if one group first includes 30 patients, over recruitment will be unavoidable and the additional patients will also be considered in the analysis. There will be no follow-up of the patients. No drop outs during the study are expected. As all the data will be collected during or immediately after treatment, we do not expect any missing values (figure 1). The Livopan study protocol was written in accordance with the STROBE statement.[9]

Data assessment

Pain is to be quantified using a 10 cm VAS.[7] Immediately after PDT, patients will be asked to record their experienced pain by pointing at a ruler graduated from 0 (no pain) to 10 (unbearable pain). The patients will be offered short interruptions from illumination if necessary. The time of the first interruption (seconds) and the number of interruptions will be noted on the case report form. Treatment will be continued after pain relief. Additionally, treatment satisfaction is to be scored immediately after PDT in patients receiving Livopan. Therefore, patients will have to fill out the German version of the TSQM.[8]

Statistical considerations

Sample size calculation

This is an explorative observational study to monitor pain reduction in patients after applying a nitrous oxide/oxygen mixture (Livopan) for pain intensity during PDT. Nevertheless, the planned sample size of n=60 is big enough to show a mean point difference of 1.47, assuming an SD of 2 (a standardised effect or Cohen's d of 0.74)[10] on the VAS with a power of 80% and a significance level of 5%.

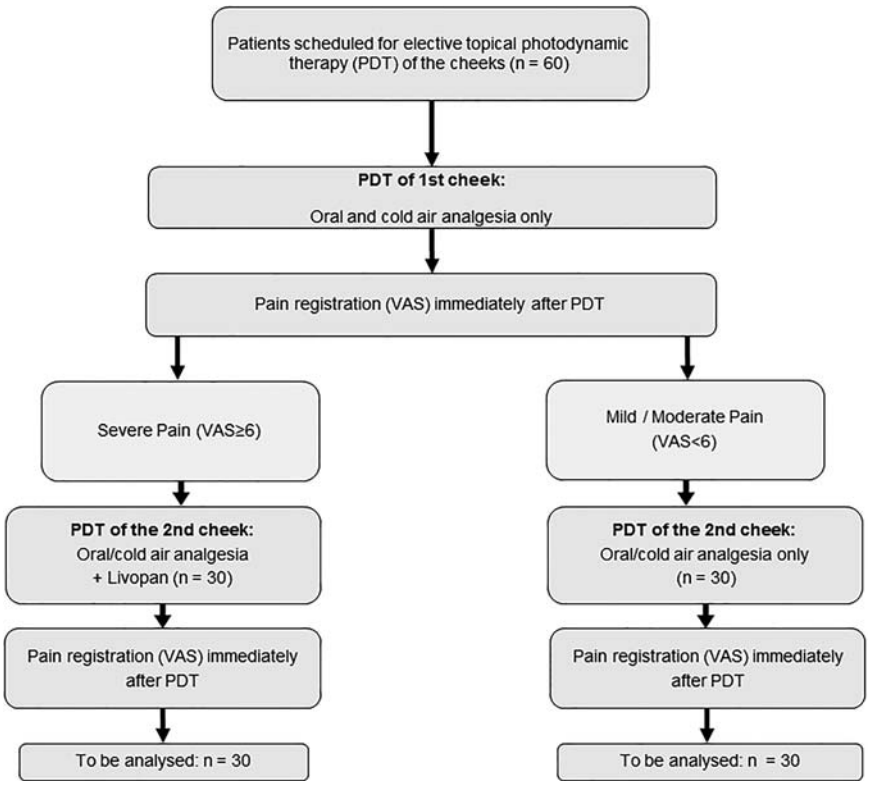

Figure 1 Flowchart of Livopan trial.

Statistical analysis

The report on findings of this observational study will be made by an explorative data analysis. First, all variables will be analysed descriptively by using the mean, SD, median, IQR, minimum and maximum. Categorical data will be described by using relative and absolute frequencies. To investigate the effect of Livopan on pain reduction, the point difference on the VAS between the treatments of the first cheek and the treatment of the second cheek will be considered, in a first step. This difference will be tested by using a one-sample t test. In a second step, this difference will be compared with the difference obtained in the control group (patients who were not offered Livopan). The difference between both groups will be compared and tested using a two-sample t test. The time to first interruption will be analysed using Kaplan-Meier estimators and log-rank-tests. The number of interruptions will be analysed using Poisson regression models. As this is an exploratory study, the findings of the statistical tests are purely descriptive and have no confirmatory character.

ETHICS AND DISSEMINATION

Declarations and ethic aspects

This study protocol was subject to critical review on the part of the persons responsible for the implementation of the study and the local ethics committee. The information contained is consistent with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013), the principles of International Conference on Harmonisation-good clinical practice (ICH-GCP) guidelines (E6) and the current laws. In the context of the approved standard operating procedures (SOPs), which are based on ICH-GCP guidelines (E6) and the German implementation of GCP for the clinical work, the patients will be informed orally and in written form about aim, character and consequences of the PDT, and the using Livopan in cases of severe pain. Before initiation of the study, the observation plan, patient information sheet and consent form were presented to the independent ethics committee. The names of patients and all confidential data are subject to professional discretion and 'Bundesdatenschutzgesetz (BDSG)'. Processing of medical data will only take place in pseudonymous form. Third persons will not be allowed insight to patient data. In case of withdrawal from the study, the data that have already been collected will be destroyed. Each participant will be informed that the participation in the study is voluntary and that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical assistance and treatment. The investigator will explain to each participant the nature of the study, its purpose, the procedure involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Additionally, all participants for the study will be provided a participant information sheet and a consent form describing the study, and providing sufficient information for participant to make an informed decision about their participation in the study. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure. The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the

signed document. The consent form must also be signed and dated by the investigator and it will be retained as part of the study records.

Risks and benefits for participants

There is no personal benefit and no additional risks for study participants. This is owed to the fact that data collection with the standardised VAS and TSQM questionnaire is the only study-related procedure. In total, the patients have to fill out two VAS questionnaires and one TSQM questionnaire within the study. This will take 5 min per questionnaire. All the other interventions and procedures during the study relate to the routine medical care of the patient according to the SOP.

Withdrawals

Patients are free to withdraw their informed consent at any time without providing a specific reason. The investigator is able to withdraw a participant for the following reasons: first, assessment by the investigator that premature termination is indicated, for example, because of a belatedly identified violation of the criteria for inclusion and/or exclusion. Second, non-compliance of the participant, which indicates the premature termination of the study.

LIVOPAN—SUMMARY OF MEDICAL PRODUCT CHARACTERISTICS[11]

Name of the medicinal product

Livopan 50%/50% medicinal gas, compressed.

Qualitative and quantitative composition

Each cylinder contains nitrous oxide (N_2O, medicinal laughing gas) 50% v/v and oxygen (O_2, medicinal oxygen) 50% v/v at a pressure of either 138 or 170 bar (15°C).

Pharmaceutical form

Medicinal gas, compressed. Colourless, odourless gas.

Clinical particulars

Therapeutic indications

Livopan is indicated for the treatment of short-term pain conditions of mild-to-moderate intensity when rapid analgesic onset and offset effects are wanted. It may be used in patients of all ages except for infants below 1 month.

Posology and method of administration

Livopan will be administered by competent personnel only. Nitrous oxide will be administered according to local guidelines and according to manufacturer's instructions. Administration of Livopan is to be given shortly before the desired analgesic effect is required. The analgesic effect is usually seen after 4–5 breaths and reaches its maximum within 2–3 min. Administration of Livopan will be continued throughout the painful procedure, or for as long as the analgesic effect is desired. Following discontinuation of the administration/inhalation, the effects wear off within a few minutes. Livopan is generally administered via inhalation in spontaneously breathing patients via a face mask. Administration of Livopan is governed by the patient's breathing. By holding the mask securely around the mouth and nose, and breathing via the mask, a so-called 'demand valve' is opened, and Livopan flows out of the equipment and is administered to the patient via the airways. Uptake occurs from the lungs.

Contraindications

In our tests, before Livopan is used, the contraindications according to the manufacturer's instructions will be carefully reviewed and safety precautions will be respected.

Contributors CF, LU and PG participated in the development and implementation of the study (sample size, protocol, submission to ethics committee, data management). LU performed the data handling and statistical analysis. CF, AE and PG helped to draft and review the paper. All authors read and approved the final manuscript.

Competing interests None.

Ethics approval Ethics approval was provided by the ethics committee of the medical faculty of the University of Heidelberg (Ethics Approval Number S-169/2014).

Provenance and peer review Not commissioned; externally peer reviewed.

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