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Impact of a nitrous oxide/oxygen mixture (LIVOPAN) on pain intensity during photodynamic therapy: Study protocol for an observational study (LIVOPAN-trial) - DRKS00006054

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Keywords: Photodynamic therapy, Livopan, pain, analgesia, laughing gas

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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 an 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 photodynamic therapy. Therefore, it remains unclear whether patients benefit from this inhalation analgesia. Within the Livopan-trial, this issue will be evaluated for the first time.

Methods and analysis Livopan-trial is a prospective, single-center, explorative, controlled, observational study to investigate the impact of Livopan on pain intensity during photodynamic therapy according to the visual analog scale in 60 patients.

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

Trial registration number 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-trial is designed as an observational study but randomized 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 randomized controlled trials.

1 INTRODUCTION

1.1 Background/Rationale

Non-melanoma skin cancer including actinic keratosis (AK) is the most common malignancy in the Caucasian population. Actinic keratosis 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 actinic keratoses, so-called "field cancerization", 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. found that 54% of patients treated with ALA discontinued treatment because of unbearable pain [3]. Several strategies for controlling pain during photodynamic therapy have been studied. Although some of them achieve a reduction in levels of pain, none was 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 to an ideal addendum in pain management. Consequently, dermatologists, pediatrics, gynecologists and dentists increasingly use Livopan [4, 5]. But to date, there are no studies evaluating the effect of Livopan on pain intensity during photodynamic therapy. Therefore, it remains unclear whether patients benefit from this procedure. Aim of the Livopan-trial is to observe the impact of Livopan on pain intensity during photodynamic therapy according to the visual analog scale (VAS) and to observe the time of the first interruption (sec) and the number of interruptions due to pain during illumination [6]. Additionally, treatment satisfaction is scored immediately after treatment using the German version of the Treatment Satisfaction Questionnaire for Medication (TSQM) [7].

1.2 Objectives

The objectives of this trial are to observe the impact of Livopan on pain intensity during photodynamic therapy according to the visual analog scale (VAS) and to observe the time of the first interruption (sec) and the number of interruptions due to pain during illumination. Additionally, treatment satisfaction is scored immediately after treatment using the German version of the Treatment Satisfaction Questionnaire for Medication (TSQM).

2 DESIGN/METHODS

2.1 Trial design

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

2.2 Recruitment and trial timeline

The estimated time frame for recruitment of 60 patients is 10 weeks. The total duration of the trial is expected to be 6 months, including analysis. Investigation of patients is expected to start in September 2014 as a single-center trial. The actual overall duration time may differ.

2.3 Trial population

60 patients with multiple actinic keratoses of both cheeks receiving an extensive treatment of the complete photodamaged area in our dermatologic outpatient department will be observed.

2.4 Criteria for Inclusion-/ Exclusion

Patients scheduled for a photodynamic therapy 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-trial.

2.5 Methods

Preparation for the illumination with red light starts with a gentle curettage of the affected area. Then the photosensitizer Metvix® (Galderma-Spirig, Egerkingen,Switzerland) is applied on the entire field, covered with occlusive dressing and protected from light by aluminum foil and adhesive bandage. After an incubation of 3 h the bandage is removed and the photosensitizer 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. The patients are offered short interruptions from illumination if necessary. All patients receive oral analgesics with 800 mg ibuprofen 30 minutes 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 photodynamic therapy starts with irradiation of one cheek. Patients experiencing a severe pain of VAS≥ 6 during PDT of one cheek, in spite of oral and cold air analgesia, will be offered an additional Livopan-analgesia for PDT of the contralateral side of the face. Livopan is administered after a critical review of potential contraindications. Recruitment of patients is performed until 60 eligible patients are included, resulting in 30 patients per group. The assumption that the number of patients per group will be balanced seems to be reasonable from our daily practical experience. Finally, 30 patients per group will be analyzed. 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 the treatment, we do not expect any missing values (see Figure 1). The Livopan-trial study protocol was written in accordance with the STROBE statement [8].

2.5.1 Data assessment

Pain is quantified using a 10-cm visual analogue scale (VAS) [6]. Immediately after PDT, patients are asked to record their experienced pain by pointing at a ruler graduated from 0 (no pain) to 10 (unbearable pain). The patients are offered short interruptions from illumination if necessary. The time of the first interruption (sec) and the number of interruptions will be noted on the case report form (CRF). Treatment will be continued after pain relief. Additionally, treatment satisfaction is scored immediately after PDT in patients receiving Livopan. Therefore, patients have to fill out the German version of the Treatment Satisfaction Questionnaire for Medication (TSQM) [7].

2.6 Statistical considerations

2.6.1 Sample size calculation

This is an explorative observational study to monitor the impact of a nitrous oxide / oxygen mixture (Livopan) on pain intensity during photodynamic therapy. Nevertheless, the planned sample size of n = 60 is big enough to show a mean points difference of 1.47 assuming a standard deviation of 2 (a

standardized effect or Cohen's d [9] of 0.74) on the visual analog scale (VAS) with a power of 80% and a significance level of 5%.

2.6.2 Statistical analysis

The report on findings of this observational study is made by an explorative data analysis. First, all variables will be analysed descriptively by use of the mean, standard deviation, median, interquartile range, minimum and maximum. Categorical data will be described by use of relative and absolute frequencies. To investigate the effect of Livopan on pain reduction, the points difference on the visual analog scale between the treatments of the first cheek and the treatment of the second cheek is considered, in a first step. This difference will be tested by use of a one-sample t-test. In a second step, this difference will be compared to the difference obtained in the control group (patients who were not offered Livopan). The difference of 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.

3 ETHICS AND DISSEMINATION

3.1 Declarations and ethic aspects

This study protocol was subject to critical review. 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 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 Good clinical practice (GCP) for the clinical work, the patients will be informed orally and in written form about aim, character and consequences of the photodynamic therapy and the use of Livopan in cases of severe pain. Before initiation of the trial the observation plan, the patient information sheet and the consent form were presented to the independent ethic committee. Ethics approval was provided by the ethic committee of the medical faculty of the University of Heidelberg (Ethics Approval Number S-169/2014). The names of patients and all confidential data are subject to professional discretion and the "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 has already been collected will be destroyed. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her 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.

3.2 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 standardized 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 minutes per questionnaire. All the other interventions and procedures during the trial relate to the routine medical care of the patient according to the standard operating procedures (SOP).

3.3 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: Assessment by the investigator that premature termination is indicated, e.g. because of a belatedly identified violation of the criteria for inclusion and/or exclusion. Secondly, non-compliance of the subject, which indicates the premature termination of the trial.

4 LIVOPAN – SUMMARY OF MEDICAL PRODUCT CHARACTERISTICS

4.1 Name of the medicinal product

Livopan 50%/50% medicinal gas, compressed.

4.2 Qualitative and quantitative composition

Each cylinder contains nitrous oxide (N2O, medicinal laughing gas) 50% v/v and Oxygen (O2, medicinal oxygen) 50 % v/v at a pressure of either 138 or 170 bar (15□C).

4.3 Pharmaceutical form

Medicinal gas, compressed. Colourless, odourless gas.

4.4 Clinical particulars

4.4.1 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 children below one month.

4.4.2 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 commenced shortly before the desired analgesic effect is required. The analgesic effect is seen after 4-5 breaths and reaches its maximum within 2-3 minutes. Administration of Livopan is 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 quickly within a few minutes. Livopan is 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.

4.4.3 Contraindications

Before Livopan is used the contraindication according to the manufacturer's instructions will be carefully reviewed and safety precautions will be respected.

5 FOOTNOTES

5.1 Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

5.2 Trial registration

The Livopan–trial is registered at the German Clinical Trial Register (DRKS): DRKS00006054

5.3 Conflicts of interest

The authors declared that they have no competing interests.

5.4 Authors' contribution

CF, LU and PG participated in the development and the implementation of the trial (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 to review the paper. All authors read and approved the final manuscript.

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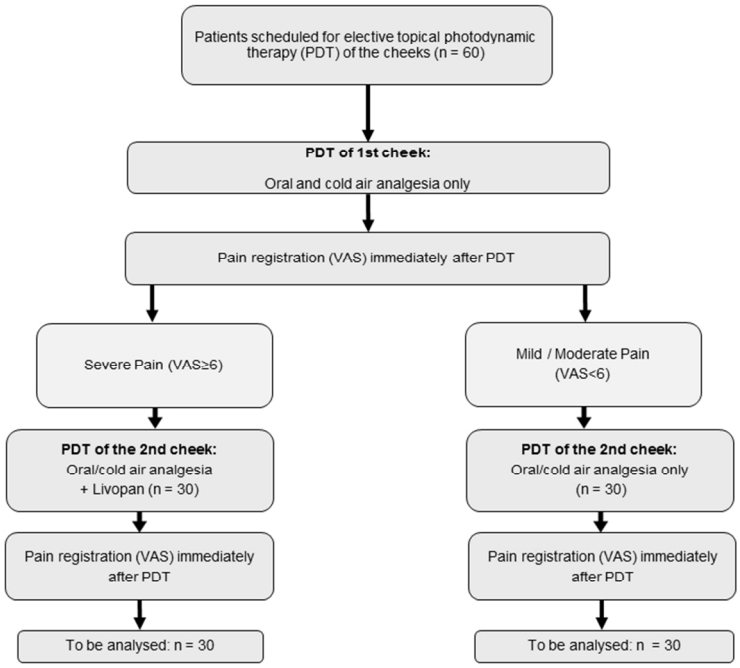

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	# 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	# 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	# 3
Objectives	3	State specific objectives, including any pre-specified hypotheses	# 3
Methods			
Study design	4	Present key elements of study design early in the paper	# 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#3 + # 4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	# 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	n.a.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	# 4
Bias	9	Describe any efforts to address potential sources of bias	n.a.
Study size	10	Explain how the study size was arrived at	# 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	# 4
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n.a.

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	# 4
		(b) Give reasons for non-participation at each stage	# 4
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	# 4
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	# 4
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n.a.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n.a.
		Cross-sectional study—Report numbers of outcome events or summary measures	n.a.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n.a.
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	n.a.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	n.a.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n.a.
Generalisability	21	Discuss the generalisability (external validity) of the study results	n.a.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	# 6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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2 DESIGN/METHODS

2.1 Study design

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

2.2 Recruitment and status of the study

Approval of Ethics Committee was granted 2014/07/28. Date of first enrollment was 2014/08/01. 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.

2.3 Study population

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Preparation for the illumination with red light starts with a gentle curettage of the affected area. Then the photosensitizer Metvix® (Galderma-Spirig, Egerkingen,Switzerland) is applied on the entire field, covered with occlusive dressing and protected from light by aluminum foil and adhesive bandage. After an incubation of 3 h the bandage is removed and the photosensitizer 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. The patients are offered short interruptions from illumination if necessary. All patients receive oral analgesics with 800 mg ibuprofen 30 minutes 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 photodynamic therapy starts with irradiation of one cheek. Patients experiencing a severe pain of VAS≥ 6 during PDT of one cheek, in spite of oral and cold air analgesia, will be offered an additional Livopan-analgesia for PDT of the contralateral side of the face. Livopan is administered after a critical review of potential contraindications. Recruitment of patients is 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, in case that one group first includes 30 patients an over recruitment will be unavoidable and the additional patients are being 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 the treatment, we do not expect any missing values (see Figure 1). The Livopan study protocol was written in accordance with the STROBE statement [8].

2.5.1 Data assessment

Pain is quantified using a 10-cm visual analogue scale (VAS) [6]. Immediately after PDT, patients are asked to record their experienced pain by pointing at a ruler graduated from 0 (no pain) to 10 (unbearable pain). The patients are offered short interruptions from illumination if necessary. The time of the first interruption (sec) and the number of interruptions will be noted on the case report form (CRF). Treatment will be continued after pain relief. Additionally, treatment satisfaction is scored immediately after PDT in patients receiving Livopan. Therefore, patients have to fill out the German version of the Treatment Satisfaction Questionnaire for Medication (TSQM) [7].

2.6 Statistical considerations

2.6.1 Sample size calculation

This is an explorative observational study to monitor the pain reduction in patients applying a nitrous oxide / oxygen mixture (Livopan) on pain intensity during photodynamic therapy. Nevertheless, the planned sample size of n = 60 is big enough to show a mean points difference of 1.47 assuming a standard deviation of 2 (a standardized effect or Cohen's d [9] of 0.74) on the visual analog scale (VAS) with a power of 80% and a significance level of 5%.

2.6.2 Statistical analysis

The report on findings of this observational study is made by an explorative data analysis. First, all variables will be analysed descriptively by use of the mean, standard deviation, median, interquartile range, minimum and maximum. Categorical data will be described by use of relative and absolute frequencies. To investigate the effect of Livopan on pain reduction, the points difference on the visual analog scale between the treatments of the first cheek and the treatment of the second cheek is considered, in a first step. This difference will be tested by use of a one-sample t-test. In a second step, this difference will be compared to the difference obtained in the control group (patients who were not offered Livopan). The difference of 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.

3 ETHICS AND DISSEMINATION

3.1 Declarations and ethic aspects

This study protocol was subject to critical review on the part of the persons responsible of 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 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 Good clinical practice (GCP) for the clinical work, the patients will be informed orally and in written form about aim, character and consequences of the photodynamic therapy and the use of Livopan in cases of severe pain. Before initiation of the study the observation plan, the patient information sheet and the consent form were presented to the independent ethic committee. Ethics approval was provided by the ethic committee of the medical faculty of the University of Heidelberg (Ethics Approval Number S-169/2014). The names of patients and all confidential data are subject to professional discretion and the "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 has already been collected will be destroyed. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her 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.

3.2 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 standardized 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 minutes per questionnaire. All the other interventions and procedures during the study relate to the routine medical care of the patient according to the standard operating procedures (SOP).

3.3 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: Assessment by the investigator that premature termination is indicated, e.g. because of a belatedly identified violation of the criteria for inclusion and/or exclusion. Secondly, non-compliance of the subject, which indicates the premature termination of the study.

4 LIVOPAN – SUMMARY OF MEDICAL PRODUCT CHARACTERISTICS

4.1 Name of the medicinal product

Livopan 50%/50% medicinal gas, compressed.

4.2 Qualitative and quantitative composition

Each cylinder contains nitrous oxide (N2O, medicinal laughing gas) 50% v/v and Oxygen (O2, medicinal oxygen) 50 % v/v at a pressure of either 138 or 170 bar (15□C).

4.3 Pharmaceutical form

Medicinal gas, compressed. Colourless, odourless gas.

4.4 Clinical particulars

4.4.1 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 children below one month.

4.4.2 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 commenced shortly before the desired analgesic effect is required. The analgesic effect is seen after 4-5 breaths and reaches its maximum within 2-3 minutes. Administration of Livopan is 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 quickly within a few minutes. Livopan is 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.

4.4.3 Contraindications

Before Livopan is used the contraindication according to the manufacturer's instructions will be carefully reviewed and safety precautions will be respected.

5 FOOTNOTES

5.1 Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

5.2 Trial registration

The Livopan-study is registered at the German Clinical Trial Register (DRKS): DRKS00006054

5.3 Conflicts of interest

The authors declared that they have no competing interests.

5.4 Authors' contribution

CF, LU and PG participated in the development and the 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 to review the paper. All authors read and approved the final manuscript.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

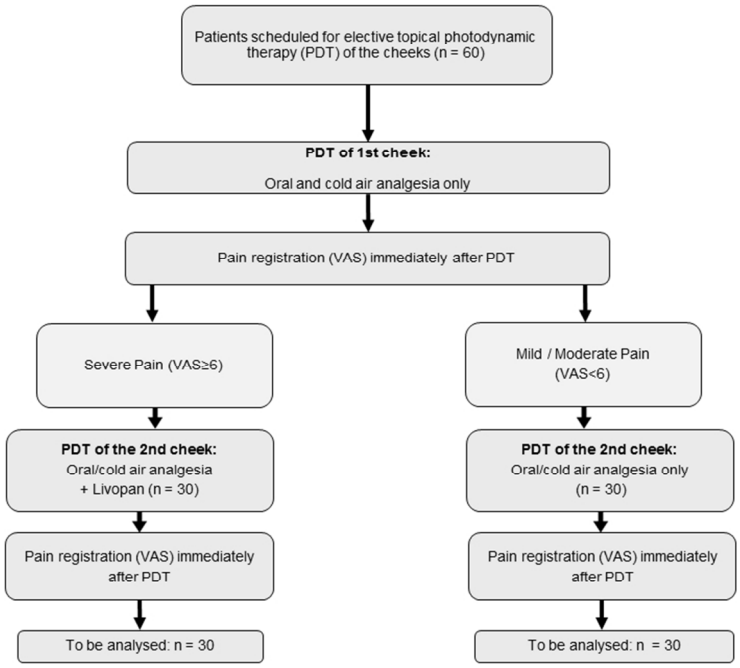
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	# 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	# 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	# 3
Objectives	3	State specific objectives, including any pre-specified hypotheses	# 3
Methods			
Study design	4	Present key elements of study design early in the paper	# 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#3 + # 4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	# 4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	n.a.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	# 4
Bias	9	Describe any efforts to address potential sources of bias	n.a.
Study size	10	Explain how the study size was arrived at	# 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	# 4
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n.a.

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	# 4
		(b) Give reasons for non-participation at each stage	# 4
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	# 4
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	# 4
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n.a.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n.a.
		Cross-sectional study—Report numbers of outcome events or summary measures	n.a.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n.a.
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	n.a.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	n.a.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n.a.
Generalisability	21	Discuss the generalisability (external validity) of the study results	n.a.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	# 6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



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