PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Pain reduction in patients applying a nitrous oxide/oxygen mixture (LIVOPAN) during photodynamic therapy: Study protocol for an observational study (LIVOPAN-study) - DRKS00006054
AUTHORS	Gholam, Patrick; Fink, Christine ; Uhlmann, Lorenz; Enk, Alexander

VERSION 1 - REVIEW

REVIEWER	Jess Tyrrell University of Exeter, UK
REVIEW RETURNED	20-Nov-2014

GENERAL COMMENTS	This is in an interesting protocol to investigate the role of LIVOPAN on pain intensity during photodynamic therapy in the treatment of AK. On the whole this protocol is well thought out. Although I do have a few comments/concerns as discussed below: 1. No consideration of treatment outcome is considered and no patient follow up - pain relief itself may lower oxygen levels in the treatment area and therefore the treatment may not be as effective. Previous studies have demonstrated that air cooling in PpIX PDT can reduce treatment efficacy. Inclusion of some outcome measure would therefore be worthwhile to allow comparison between Livopan and other pain relief measures. 2. One limitation you have not discussed is the level of PpIX accumulated. Differential accumulation within the two cheeks could result in differential pain and therefore might bias your results. Do you have a way of monitoring PpIX level? Or perhaps a comparison between pain in L and R cheek in those who do not require Livopan - is it similar? 3. The assumption that of the 60 people you will have exactly 30 in each group concerns me - what plans are in place if this is not the case? Over recruit in one group until you reach 30 in each? 4. What is rationalisation for looking at AK on cheeks? Any particular evidence around pain in this area?

REVIEWER	Chaves, Yuri Universidade de São Paulo-SP
REVIEW RETURNED	19-Dec-2014

GENERAL COMMENTS	I suggest randomizing the cheeks that will be irradiated.

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1

4. No consideration of treatment outcome is considered and no pa-tient follow up - pain relief itself may lower oxygen levels in the treat-ment area and therefore the treatment may not be as effective. Previ-ous studies have demonstrated that air cooling in PpIX PDT can reduce treatment efficacy. Inclusion of some outcome measure would there-fore be worthwhile to allow comparison between Livopan and other pain relief measures."

Treatment outcome (in regard to response rate/efficacy) of PDT is definitely a very important potential study endpoint. For evaluation a follow-up of at least 12 weeks is needed. Indeed, as mentioned above different studies shows that the use of air cooling as pain relief results in a significantly decreased photobleaching of protoporphrin IX during PDT and subsequently leads to a reduced efficacy of PDT treatment. It is proposed that the low temperature of air may cause local vasoconstriction, reducing reactive oxygen singlets production and thus limiting clinical effectiveness. Therefore, tumor clearance 3 months post treatment is a very important potential study endpoint that should be considered in future studies evaluating the impact of the nitrous oxide/oxygen mixture with an adequate follow-up period.

5. „One limitation you have not discussed is the level of PpIX accumu-lated. Differential accumulation within the two cheeks could result in differential pain and therefore might bias your results. Do you have a way of monitoring PpIX level? Or perhaps a comparison between pain in L and R cheek in those who do not require Livopan - is it similar?)."

Differential PpIX accumulation within the two cheeks is another point of equal importance, because there is the possibility of unequally severe damage of the skin of the left and right cheek. To minimize the potential bias the sides in the group treated with Livopan analgesia will be consecutively alternated and the patients in the group that do not require Livopan will serve as a control group.

6. „The assumption that of the 60 people you will have exactly 30 in each group concerns me - what plans are in place if this is not the case? Over recruit in one group until you reach 30 in each?"

Our experience with pain evaluation in former studies has shown that approximately one-half of the patients are experiencing a pain of VAS≥ 6 during PDT according to the visual analog scale (VAS). In case that one group first reaches 30 patients an over recruitment will be unavoidable. Nevertheless, the additional patients are being considered in the analysis. In section "2.5 Methods" of the manuscript this issue is being considered on page 4 (line 26 – 33).

7. „What is rationalisation for looking at AK on cheeks? Any particular evidence around pain in this area?"

In our dermatologic outpatient department patients with multiple actinic keratoses are being scheduled for a photodynamic therapy. Actinic keratosis is an early in situ squamous cell carcinoma with the possibility to transform into the dangerous invasive squamous cell carcinoma, which has metastatic potential. Hence, it is a common consensus that actinic keratoses have to be treated.

A study by Gholam et al. shows that pain intensity is de-pendent on location of the treated field. During treat-ment, mean visual analog scale scores ± SEM of the dif-ferent locations were 2.5 ± 0.36 (hand), 3.6 ± 0.35 (occi-put), 5.2 ± 0.19 (forehead), 5.9 ± 0.20 (cheeks)[Gholam P, Denk K, Sehr T et al. Factors influencing pain intensity dur-ing topical photodynamic therapy of complete cosmetic units for actinic keratoses. J Am Acad Dermatol. 2010 Aug;63(2):213-8.]

Comments from Reviewer 2

8. "I suggest randomizing the cheeks that will be irradiated."

To minimize the potential bias of differential PpIX accumulation within the two cheeks the sides in the

group treated with Livopan analgesia will be consecutively alternated. However, randomization would be preferable and should be considered in future studies.