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CLINICAL REPORT

Morphine Gel 0.3% Does Not Relieve Pain During Topical Photodynamic Therapy: A Randomized, Double-blind, Placebo-controlled Study

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There is a demand for pain relief during photodynamic therapy. We therefore investigated the efficacy and side-effects of topical morphine gel 0.3% for pain relief during topical photodynamic therapy in a randomized, double-blind, placebo-controlled study. The study involved 28 patients with actinic keratoses or basal cell carcinomas. Each patient was treated with photodynamic therapy after superficial curettage of 2 treatment areas that were randomized to morphine gel or placebo gel. The gels were applied 15 min before illumination. Pain was assessed pre-illumination, during, and immediately after illumination, using a numeric rating scale. Skin redness was determined by reflectance spectrophotometry and the size of the treated area by protoporphyrin IX fluorescence. There were no differences between the areas according to accumulation of protoporphyrin IX (p =0.34), size of fluorescence areas (p =0.84), or skin redness (p =0.95). There was no significant pain relief of topical morphine gel compared with placebo gel (p >0.23). This negative result suggests that opioid receptors may not be involved in the pain induced by photodynamic therapy. ***Key words: topical photodynamic therapy; pain; morphine; actinic keratosis; basal cell carcinoma.***

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Topical photodynamic therapy (PDT) is a well-established treatment for actinic keratoses (AK) and basal cell carcinomas (BCC), using the topical photosensitizers 5-aminolevulinic acid (5-ALA) or the methyl ester (methyl aminolevulinate) (MAL) (1–3). The treatment is generally well tolerated. However, frequent side-effects are pain and post-treatment erythema and oedema (2, 4). PDT-related pain is usually described as "stinging", "prickling" and "burning" (1–3). There is a large variation in pain intensity, and sometimes pain may limit the patient's compliance (5). The degree of pain depends on the light source, the light delivery, skin temperature and the photosensitizer (3, 6–7). Strategies to reduce pain include topical or injected local anaesthetics, premedication with benzodiazepine, the use of hand-held ventilators, and water spray during illumination, mostly with limited success (2, 8).

Opioid receptors have been identified in peripheral tissues and it has been suggested that topically applied opioids may have a local action (9–10). Opioid receptors are not obvious in normal tissue, but appear within minutes to hours after the start of an inflammatory process (9, 11). Topical opioids have been used for a number of painful skin conditions (9, 12–14), including epidermolysis bullosa, pressure ulcer, leg ulcer and cutaneous cancer pain, but have not been used together with PDT. This study was performed to assess the effect of morphine gel on pain relief during PDT and, secondarily, to study the local and general tolerance to morphine gel.

MATERIALS AND METHODS

Participants

Twenty-eight patients with 2 areas of BCC (n =1 patient) or AK (n =27 patients) within the same anatomical area were included. Maximum sizes of the treated areas were 9×10 cm. A dermatologist confirmed the diagnoses by clinical examinations. Median age was 72 years (range 44–87 years). Exclusion criteria were psychiatric diseases, and the use of analgesia during PDT. Written informed consent was obtained from all participants. The local Ethics Committee approved the protocol (KF 01–128/04).

Study design

The study design was a within-patient randomized, double-blind, placebo-controlled trial using concealed envelopes for the randomization procedure. The 2 treatment areas in each patient were randomized to receive either morphine gel 0.3% or placebo gel. A laboratory technician prepared the morphine gel 0.3% by mixing morphine sulphate BP 30 mg/3 ml with IntraSite gel 7 g (Smith & Nephew Healthcare Ltd, Middlesex, UK). The placebo gel was a mixture of IntraSite gel 7 g and 3 ml isotonic NaCl. Each product was mixed for 3 min and prepared within 1 h before application (15).

Photodynamic therapy

Two areas of less than 9×10 cm (90 cm^2) were prepared with superficial curettage as recommended for MAL-PDT (Metvix®, Photocure ASA, Oslo, Norway) (1). Metvix was applied in a

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1-mm thick layer under occlusive dressing (Tegaderm, 3M) for 3 h, and then removed with saline and non-woven gauze. Thereafter morphine and placebo gels were applied to the areas and after 15 min the gels were removed prior to illumination.

The light source (Aktilite™ 128, PhotoCure ASA) delivered red light centred at 634 nm (full-width half-maximum 18 nm), with a total dose at 37 J/cm^2. The illumination time was about 9 min with a distance of 7 cm from the skin. Both areas were treated simultaneously. During illumination the patients were not allowed to receive pain relief except for breaks, which were registered.

Outcome measures

Pain was assessed by a numeric rating scale (NRS), where 0 was no pain and 10 was the worst imaginable pain. The assessments were performed simultaneously in both areas just before (0 min), during (3 and 6 min), and immediately after illumination (9 min). NRS (verbal) was chosen because the patients were blinded by protective glasses through the assessment, and therefore could not use the graphically visual analogue scale. Verbal numerical scales correlate well with conventional visual analogue scales (16–18). Moreover, patients were in telephone interviews 24 h after PDT asked about local (redness, itch, oedema) or systemic (nausea, sedation, dizziness) side-effects.

Skin redness was determined by a skin reflectance meter (UV-Optimize, Model Matic 555, Matic, Naerum, Denmark) before curettage because it is presumed that the mechanisms of the opioid receptors action are upregulated in inflamed tissue (9, 11).

To identify the size of the affected lesions, protoporphyrin IX (PpIX) skin fluorescence intensity was measured in fluorescence images (Medeikonos PDD/PDT model 101, Medeikonos, Göteborg, Sweden).

Statistics

Normally there is a large variation in pain scores during PDT, therefore we used a set-up with patients as their own controls. A reduction in pain score was chosen to 1.5 as the smallest detectable. Earlier studies have shown a standard deviation of 2 in pain score. Having a test power of 0.80 and a significance level of 0.05, 28 patients were needed to complete the study.

Since not all outcome data were normally distributed, non-parametric Wilcoxon signed rank test was used. p-values less than 0.05 were considered significant. All analyses were done in SPSS for Windows (SPSS version 11.51, SPSS Inc., Chicago, USA).

RESULTS

Twenty-eight patients completed the study. Pain scores before, during and immediately after illumination are shown in Table I. There were no significant differences in pain scores between morphine- and placebo-treated areas. The maximum pain scores were identical (5.5 vs. 5.5) in the 2 areas.

There was no difference in accumulation of PpIX between morphine and placebo treated areas ($p = 0.35$) as measured by fluorescence intensity (data not shown) and the fluorescence areas were similar (median, morphine 59.6 cm^2 and placebo 59.2 cm^2) ($p = 0.84$). Inflammation measured as skin redness before curettage was similar in the morphine- (median 40.1% on skin reflectance meter) and placebo-treated (median 37.0%) areas ($p = 0.95$) and significantly higher than in surrounding skin (median 25.0%–26.4%) ($p < 0.001$).

Table I. *Pain scores (numeric rating scale; NRS) between morphine gel- and placebo gel-treated areas before (0 min), during (3 and 6 min), and immediately after (about 9 min) topical photodynamic therapy (PDT) together with maximum pain intensity scores (n =28). Data are shown as median and interquartile range (IQR 25–75%)*

Treatment with PDT (min)	0	3	6	9	Max. NRS
Morphine	0 (0–0)	5 (3.8–7)	4 (3.8–6)	5 (4–7)	5.5 (4–7)
Placebo	0 (0–0)	4.5 (2.8–7)	4 (3–6.3)	5 (3–7)	5.5 (3.8–7)
p-value	0.71	0.23	0.67	0.48	0.49

Four patients needed breaks of 1–5 min during illumination due to severe pain. In the case of breaks, both areas were treated identically. Twenty-four hours after treatment similar local adverse effects were reported in the 2 groups. Twenty-four patients reported skin redness, 9 patients oedema and 4 patients itching. No systemic (nausea, sedation, dizziness) effects were reported.

DISCUSSION

There have been several attempts to reduce PDT-related pain, e.g. by topical anaesthesia with EMLA® cream, infiltrating and spraying with lidocaine, spraying with cold isotonic saline or water, or by pausing during light exposure. Only injected local anaesthetics reduced the pain to a tolerable level. Application of topical analgesics, such as mixtures of lidocaine/prilocaine, during the incubation period of ALA/MAL is not recommended as their high pH values might chemically inactivate the photosensitizer (1). Pagliaro et al. (19) describe in a pilot study use of cold air analgesics as effective in the reduction of pain, but only in the second of 2 treatments. In this study we use topical morphine, which was not effective for pain relief during PDT.

The use of topical morphine for a number of painful conditions has been reported in several case studies. The concentration of topical morphine has been arbitrarily chosen from 0.008% to 0.3% (9). In 2003, Zeppetella et al. (13) presented the first randomized, double-blind, placebo-controlled, cross-over pilot study of painful ulcers, which demonstrated significant and relatively long-lasting analgesia. However, Vernassiere et al. (10) recently concluded that topical morphine, cannot be an alternative to morphine administered by other routes in painful chronic skin ulcers.

Pain during topical PDT probably involves nerve stimulation and/or tissue damage (1–3, 6). Pain relief during PDT should minimize PpIX in nerve endings, desensitize nerve endings or block the nerve depolarization. Morphine may act by desensitizing nerve

endings, but this is obviously not sufficient to reduce pain, even though opioid analgesics are more effective under inflammatory conditions, as in this study (measured redness) (9, 11).

PDT-related pain is described as "stinging", "prickling" and "burning", which is the typical pattern of postoperative pain ("first pain", which is ascending through the A delta fibres and a "second burning pain" ascending though C fibres) and of neuropathic pain. First pain sensation is presumed to result from activation of myelinated nociceptive afferents and is not highly sensitive to modulation by systemic opioids, which may explain the lacking effect in this study (20). First pain is treated with, e.g. blockade (epidural anaesthesia), which is not a realistic treatment for pain during PDT. Neuropathic pain should primarily be treated with e.g. tricyclic antidepressive and ion channel blocker, which is not realistic for pain of short duration (11, 20–21).

The lack of pain relief by morphine gel might also be explained by the treatment regime. The contact of the morphine gel with the lesion might have been too short or the absorption of the gel into the lesions may be insufficient. However, the gels could not be applied before application of MAL, and the gels had to be removed before illumination, since a pre-study showed a light absorption of the gels of approximately 50%.

This study does not support the use of morphine gel for topical pain relief during topical PDT for lesions of BCC and AK.

Conflict of interest: None reported.

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