Photodynamic therapy - pain and aspects of pain relief

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2011

UNIVERSITY OF GOTHENBURG

Cover: Photodynamic therapy of actinic keratoses
(Informed consent obtained, photo: Christina Halldin)

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ISBN 978-91-628-8388-1
http://hdl.handle.net/2077/26592

Printed by Kompendiet, Göteborg, Sweden 2011

To my family

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ABSTRACT

Photodynamic therapy (PDT) is a non-invasive treatment option for superficial basal cell carcinoma (BCC), squamous cell carcinoma (SCC) in situ or Bowen's disease (BD), and actinic keratoses (AK). One of the advantages of PDT is the possibility to treat field cancerization. PDT is also suitable to use when treating poor healing areas such as the lower extremities. Furthermore, PDT offers an excellent cosmetic outcome compared with conventional therapies. In general the treatment is well tolerated, side effects such as erythema, scaling and crusts are normal after treatment. The most problematic side effect is pain, especially when large areas of extensive AKs are treaded in the face and/or scalp.

The overall aim of this thesis was to investigate and identify factors of pain associated with PDT, and try to achieve effective methods to reduce the pain during treatment.

In the first study (Paper I), 377 patients treated with PDT during the year 2004 were investigated. Of special interest was the patients' pain experience and identifying pain predictors. The strongest predictor of pain during PDT was size of the treated area, followed by diagnosis and location.

In Study II (Paper II), we examined transcutaneous electrical nerve stimulation (TENS) as a method of pain relief during PDT. During treatment the strength of the stimulation was controlled by the patient. The result of the TENS stimulation was a minor decrease in pain during PDT compared with the patient's previous pain assessments without TENS.

In Study III (Paper III), the pain-relieving effect of frontal nerve block (NB) in combination with occipital NBs was examined. The NBs were applied unilaterally in the occipital and frontal area, with the other side of the face serving as the patient's own control. In the nerve-blocked area the mean VAS score was 1.0 during PDT, compared with 6.4 on the non-blocked side. One limitation was that the temple area is not completely covered by current NBs.

Finally, in Study IV (Paper IV), the patients, being the PDT users, were interviewed about how they experienced and perceived PDT. All interviewees had been treated for AKs with PDT on the face and scalp and had undergone PDT with and without NB. The patients had experienced the pain as very intense without NB but said that the result in the end had made it worth it. The NBs had given satisfactory relief from pain; however, the injections could be transiently painful.

Key words: actinic keratosis (AK), field cancerization, interviews, nerve block (NB), pain, photodynamic therapy (PDT), transcutaneous electrical nerve stimulation (TENS)

ISBN 978-91-628-8388-1, hptt://hdl.handle.net / 2077 / 26592 Gothenburg 2011

LIST OF PAPERS

This thesis is based on the following papers, which are referred to the text by their Roman numerals:

I Halldin CB, Gillstedt M, Paoli J, Wennberg A-M, Gonzalez H. Predictors of pain associated with photodynamic therapy: a retrospective study of 658 treatments. Acta Derm Venereol. 2011;91(5):545–51.

II Halldin CB, Paoli J, Sandberg C, Ericson MB, Wennberg A-M. Transcutaneous electrical nerve stimulation for pain relief during photodynamic therapy of actinic keratoses. Acta Derm Venereol. 2008;88(3):311–3.

III Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg A-M. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. Br J Dermatol. 2009 Apr;160(4):795–800.

IV Halldin CB, Gonzalez H, Wennberg A-M, Lepp M. Patients' experiences of pain and pain relief during photodynamic therapy of actinic keratoses. Submitted for publication.

CONTENTS

ABBREVIATIONS

AK	actinic keratosis
ALA	aminolaevulinic acid
ATP	adenosine triphosphate
BCC	basal cell carcinoma
BD	Bowen's disease
CoA	coenzyme A
DNA	deoxyribonucleic acid
FC	ferrochelatase
IASP	International Association for the Study of Pain
J	joule
LED	light emitting diode
LIA	local infiltration anesthesia
MAL	methyl aminolevulinate
MM	malignant melanoma
NB	nerve block
NMSC	non-melanoma skin cancer
NRS	numeric rating scale
PBGD	porphobilinogen deaminase
PDT	photodynamic therapy
PpIX	protoporphyrin IX
ROS	reactive oxygen species
SCC	squamous cell carcinoma
SD	standard deviation
SEM	standard error of mean
SIA	subcutaneous infiltration anesthesia
TENS	transcutaneous electrical nerve stimulation
TRPV1	transient receptor potential cation channel subfamily V member 1
TRPM8	transient receptor potential cation channel subfamily M member 8
VAS	visual analogue scale
VIS	visible light
VPL	variable pulse light
VRS	verbal rating scale
wIRA	water-filtered infrared A light

1. INTRODUCTION

Light has been used in treating different human diseases since ancient Egypt, India and China. Use of phototherapy and, later on, photodynamic therapy (PDT) started with the Danish scientist Niels Finsen in the 1890s. Finsen successfully treated patients suffering from lupus vulgaris (skin tuberculosis) with sunlight and artificial light. For this discovery, he was awarded the Nobel Prize in 1903. The effect of a drug and light combination was first investigated by Raab and Von Tappeiner in the early 20th century. Examining the toxic effect of quinine on malaria protozoa during a thunderstorm, they detected that lightning had an increased toxic effect on the protozoa.[1, 2] Further investigations led to the discovery that oxygen was necessary for the photodynamic effect. Experimental use of photosensitizers (haematoporphyrin and haematoporphyrin derivate) was performed in the early 1910s in both animals and humans by the German doctor Meyer Betz who, among other experiments, gave himself injections of haematoporphyrin with the result of being very photosensitive for over 2 months.[3]

The overall aim of this thesis was to investigate and identify factors of pain associated with PDT, and try to achieve effective methods to reduce the pain during treatment.

In Study I (Paper I), pain predictors and the patients' experiences of pain during PDT were investigated. Transcutaneous electrical nerve stimulation (TENS) was examined as a pain relief method during PDT in Study II (Paper II). In Study III (Paper III), frontal nerve block (NB) in combination with occipital NBs was examined. Finally, the patients, being the actual PDT users, were interviewed about how they experienced and perceived PDT (Paper IV).

1.1 The human skin

The human skin covers a surface area of 1.5–2 m^2 and weighs 4–5 kg, which makes it the largest organ of the human body. The functions of the skin are to protect the body from water loss (dehydration), regulate the body temperature and be a sense organ for heat, cold, pain and touch. The skin is also a barrier against bacteria and viruses and gives protection against ultraviolet radiation. Synthesis of vitamin D also takes place in the skin.

The skin consists of three layers: the epidermis, the dermis and the subcutis (Fig. 1). The most superficial layer is the epidermis whose thickness varies between 0.05 mm and 1 mm, being the thinnest on the eyelids and the thickest on the palms and soles. The epidermis itself consists of several layers of keratinocytes but also of melanocytes, Langerhans cells and Merkel cells.

The deepest part of the epidermis is the stratum basale, a layer that contains immature keratinocytes. When these cells divide and mature they migrate to the more superficial layers, first to the stratum spinosum and then to the stratum granulosum where these cells become more flat and extended. The stratum corneum is the most superficial layer and consists of corneocytes (flat keratinocytes with no nuclei). The stratum corneum is a semi-permeable barrier that protects the body from water loss. Other cells of the epidermis are the melanocytes, located in the stratum basale. They have irregular extensions, which can reach the stratum spinosum. The melanocytes contain pigment that gives the skin its colour and provides some protection against deoxyribonucleic acid (DNA) damage due to ultraviolet radiation.

The star-shaped Langerhans cells situated mainly in the stratum spinosum have a significant role in the immunological reactions in the skin, presenting antigens to T-lymphocytes. The Merkel cells have a role in the peripheral nerve system as they respond to touch.

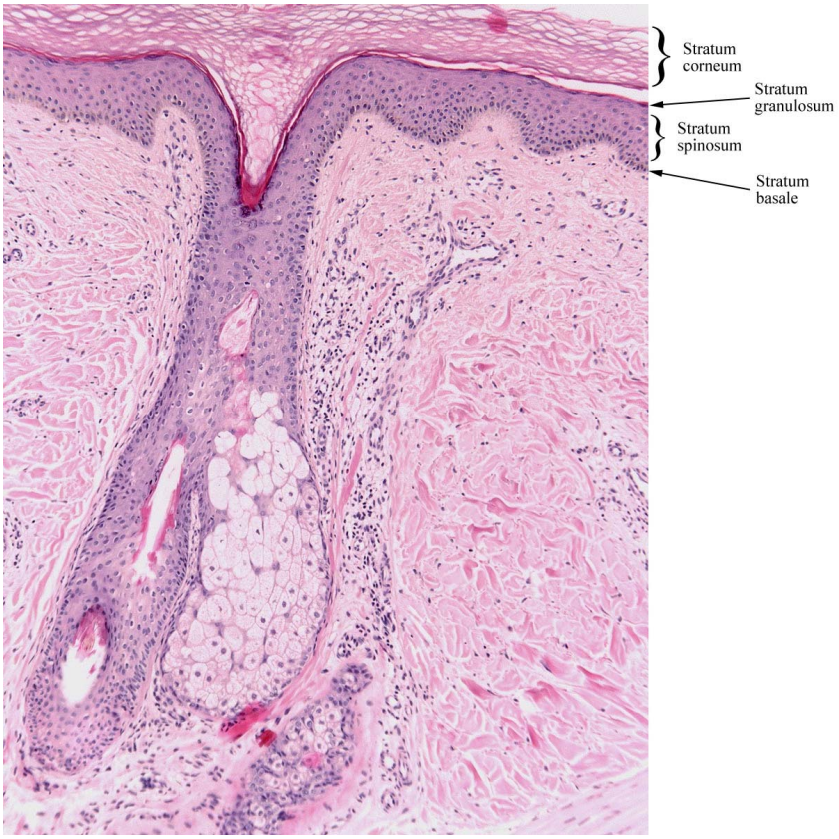


Figure 1. Skin anatomy (Photo: Lena Mölne)

The dermis and epidermis are separated by the basal membrane at the dermo-epidermal junction. The dermis consists of fibres of elastin, collagen and reticulin surrounded by a liquid ground substance providing the skin with elasticity and

strength. The dermis contains both blood vessels, supplying the epidermis and dermis with nutrients and oxygen, and lymph vessels. The subcutis is the deepest layer of the skin. It mainly consists of lipocytes and some blood vessels. The functions of the subcutis are as a reserve energy source, as well as thermal insulation and trauma protection.[4]

The skin is densely innervated by afferent sensory and efferent autonomic nerve branches. The sensory nerve endings are divided into tactile corpuscles and free nerve endings. In the epidermis there are free nerve endings and the nerve endings are also in contact with the Merkel cells in the deeper part of the epidermis.

How quickly the impulses are transmitted in the sensory nerves depends on whether the nerves are myelinated or unmyelinated. The myelinated thicker cutaneous nerves (1-20 μm) have been diverted in Aβ- and Aδ fibres due to their conduction velocities corresponding to 35-75 m/s and 5-20 m/s respectively. The unmyelinated thinner C-fibres (0.2-1.5 μm) are slower with the velocity of conducting 0.1-2 m/s. Some authors believe that in the fast acute pain with a well localized pain, the pain is mediated by the A fibres and the more diffuse throbbing pain is mediated by the C-fibres.[5] This pain usually comes later.

1.2 Skin cancer

Skin cancer is divided into two main categories, malignant melanoma (MM) and non-melanoma skin cancer (NMSC). This thesis will focus on NMSC.

1.2.1 Malignant melanoma

Malignant melanoma originates from a mutated melanocyte either within a pre-existing nevus or in normal skin (de novo). The most common types of MMs are superficial spreading melanoma, lentigo malignant melanoma, nodular melanoma and acral lentiginous melanoma, and there are also in situ types of melanoma. When the malignant melanocytes begin invading the dermis they have metastatic potential.[6] Malignant melanomas are the most serious type of skin cancer, with higher risks of metastasizing compared with NMSC and consequently increased risk of mortality. In Sweden, out of 9 million inhabitants, approx. 2,500 patients are diagnosed with MM each year and MM is the cause of death of approx. 450 patients annually.

1.2.2 Non-melanoma skin cancer precursors

Actinic keratoses

Actinic keratoses (AKs) are early precursors of squamous cell carcinoma (SCC). Up to 10% of all AKs can develop to an invasive SCC, but many remain unchanged and spontaneous regress is seen in 25% of the lesions.[7] AKs usually occur on sun exposed skin areas.[8] AKs can be divided into hypertrophic, pigmented and lichenoid AKs. Actinic cheilitis is AKs on the lips. The term “field cancerization” is used for sun damage of extensive skin areas with multiple pre-cancerous lesions that have a potential of developing into SCC.

Opinions among physicians differ about whether AKs are lesions that need to be treated. The general opinion (which our clinic supports) is that AKs are precursors to SCC and consequently must be treated.[9-11] However, some physicians do not find it necessary to treat AKs since they rarely develop into SCC. [12, 13]

Squamous cell carcinoma in situ

Squamous cell carcinoma in situ (SCC in situ) or Bowen's disease (BD) is the final SCC precursor. It presents as atypical keratinocytes that have not entered the dermis and are found in the entire epidermis.[14, 15] These lesions are common in sun-exposed areas such as the cheeks, ears and extremities.

1.2.3 Non-melanoma skin cancer

Squamous cell carcinoma

Squamous cell carcinomas derive from atypical keratinocytes in the epidermis. Most SCCs are slow-growing lesions invading the dermis. There is a risk of spreading to regional lymph nodes and from there to other organs.[16] The annual incidence of SCC in Sweden is 4,500 patients with a mortality of approx. 65 patients each year. The likelihood of presence of AKs is almost 100% when a SCC has occurred on the skin, indicating that AKs need to be treated.

One large risk group for developing SCCs are organ transplant recipients, as a result of their immune suppressant medication. The incidence in this group is about 100 times higher than in an immunocompetent population.[17, 18]

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer, representing about 80% of all NMSC cases. Basal cell carcinomas are thought to originate de novo. These tumours grow slowly, eventually invading surrounding tissue and underlying structures, but they very rarely metastasize. There are three main forms of BCCs based on their histological growth: superficial, nodular and infiltrating (morpheiform).

1.3 Treatment of non-melanoma skin cancer and its precursors

Several different treatment options are available for treatment of NMSC and its precursors.

1.3.1 Surgery

Surgery is the golden standard for treatment of MMs, SCCs and BCCs.[19-21]

When treating infiltrative morpheiform BCCs with borders that are difficult to identify, Mohs micrographic surgery is recommended.[22, 23]

1.3.2 Destructive methods

There are destructive methods available, such as cryosurgery[24] (with or without curettage) and curettage followed by electrodessication.[25] This is suitable for superficial lesions such as AKs, SCC in situ and some BCCs.[23] Destructive methods are easily performed under local anaesthesia. However, there is a risk of developing hypo/hyperpigmentation or scarring due to the treatment.

1.3.3 Topical drugs

Topical drugs such as 5-fluorouracil, diclofenac and imiquimod can be used on AKs (field cancerization), imiquimod can also be used for superficial BCCs.[26, 27] The drugs are applied for several weeks and a disadvantage of the treatment could be erythema, scaling and erosions on the treated area lasting several weeks. There is a risk that the patient is not as compliant as instructed and consequently of the treatment being less effective.

1.3.4 Systemic treatment with hedgehog inhibitors

The hedgehog pathway is important for cell growth during embryonic development. In adults this pathway normally is inactive but in BCCs the pathway can be activated by mutations.[28] This discovery may lead to development of a new treatment possibility, using hedgehog pathway inhibitors. These may be used in treatment of severe BCCs.[29]

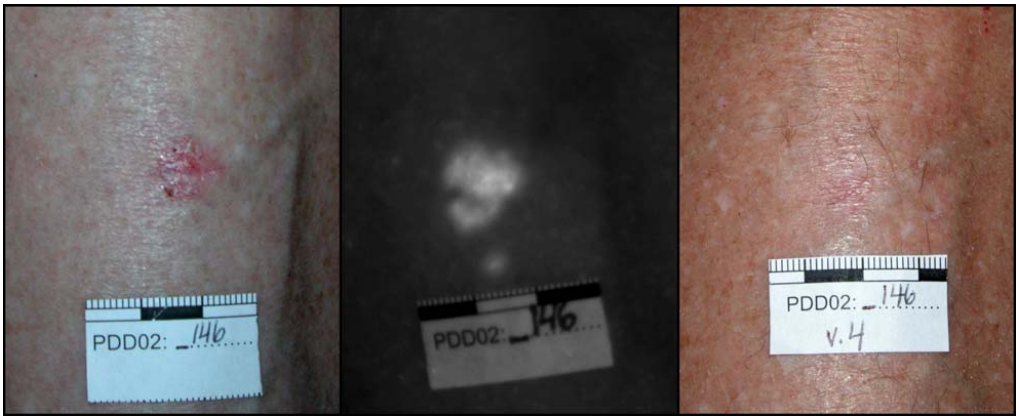
1.4 Photodynamic therapy

Photodynamic therapy is a non-invasive treatment option for BCCs, AKs and SCC in situ.[30, 31] The advantages of PDT are the possibility to treat field cancerization and the assurance of a good compliance. Photodynamic therapy is suitable for treating poor healing areas such as the lower extremities.[32] Furthermore, PDT offers an excellent cosmetic outcome compared with conventional therapies.[33] Another advantage is the possibility to repeat the treatment if required.

Photodynamic therapy can also be used in several other diseases and locations, e.g. treatment of age-related macular degeneration in the eye, brain tumours such as glioblastomas, urological diseases and head and neck cancers.[34] Photodynamic therapy is not appropriate in the treatment of pigmented lesions due to the fact that the pigment melanin absorbs the light. In these lesions, surgery is the only option, which also enables a histopathological diagnosis

Sometimes the border of a tumour may be difficult to identify, fluorescence diagnostics may then be used for tumour demarcation, e.g. prior to surgery or research purposes.

By recording the red PpIX fluorescence of the lesion during illumination with blue light (405 nm) the lesion can be visualized[35] fig. 2.



1) 2) 3)

Figure 2. 1) Superficial basal cell carcinoma 2) fluorescence image 3) treatment outcome (Photo: Christina Halldin)

1.4.1 History of photodynamic therapy

After the discoveries in the early 20th century, knowledge about the photodynamic effect appeared to be forgotten and for a long time no further development was made in the photodynamic field.

In the 1970s and 1980s Dougherty and his colleagues at the Roswell Park Cancer Institute, Buffalo, TX, USA, resumed the study and development of PDT. The use of photosensitizers developed further from a haematoporphyrin derivate administered systemically, to a product called Photofrin, which still is in clinical use.[36]

In 1990 Kennedy and Pottier presented their results using a phorphyrin precursor, δ-5-aminolaevulinic acid (ALA), as a photosensitizer in the treatment of superficial BCCs in combination with illumination with visible light (VIS).[37] Their presentation was the start of a new, more modern approach to PDT, and ALA is still in use although in Scandinavia its methyl ester, methyl aminolaevulinate (MAL), is more commonly used. In Sweden, MAL is the only approved photosensitizer for PDT and ALA can solely be used for research purposes.

1.4.2 Performing photodynamic therapy

Photodynamic therapy is based on three main parts that must be present: a lesion-localizing photosensitizer, a light source with an appropriate wavelength, and oxygen. Light curettage without bleeding is performed on the area of treatment to ensure better penetration. A pro-drug (ALA or MAL) is applied to the lesion in an approximately 1 mm thick layer with a surrounding area of 1 cm minimum of apparently healthy skin. The treatment area is covered with an occlusive dressing for 3 hours (MAL). The photosensitizer accumulates in rapidly dividing cells such as pre-cancer or cancer cells. After 3 hours the dressing and excess cream are removed

and the illumination with visible red light starts. During the illumination an energy transfer between the sensitizer and molecular oxygen occurs and reactive oxygen species (ROS), mainly singlet oxygen, are formed. The target cells are then destroyed.[38]

1.4.3 Photosensitization

When MAL is applied to the skin the intracellular enzymes de-esterify MAL to ALA. [39] The final photosensitizer, protoporphyrin IX (PpIX), is endogenously formed by haem biosynthesis in the cells. (Fig. 2)

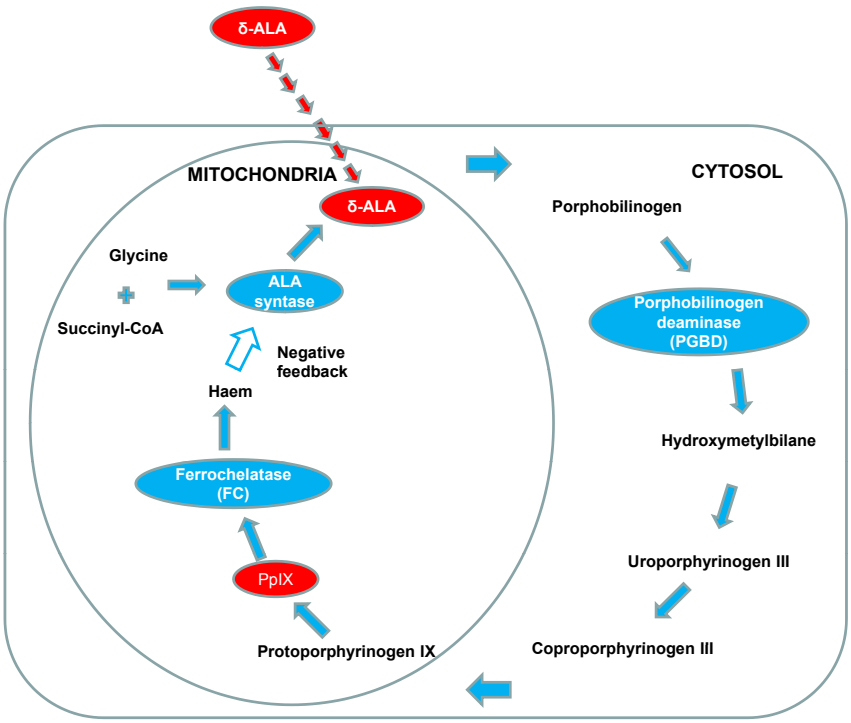


Figure 3. Haem biosynthesis (Figure: Christina Halldin)

Aminolaevulinic acid is synthesized from glycine and succinyl-coenzyme A (CoA). There are rate-limiting steps in the formation of ALA and by adding exogenous ALA the first step is bypassed. The regulation by negative feedback from the last step when iron is involved in building haem is also bypassed when ALA is supplied in excess. More PpIX can be formed and accumulated in the tumour cells.[39] The more selective accumulation of PpIX in tumour cells is thought to be due to the increased enzyme activity in porphobilinogen deaminase (PBGD) and a decreased activity of ferrochelatase (FC) in tumour cells. [40] In addition, the altered skin barrier in tumour cells may also help the more rapid accumulation of PpIX in the tumour cells compared with normal cells. The formation of PpIX in normal cells is slower and therefore these cells are not accessible by the photochemical reaction due to insufficient accumulation of PpIX.

1.4.4 Light sources for photodynamic therapy

There are several different light sources that can be used when performing PDT.[41]

Light-emitting diodes

The light-emitting diode (LED) lamps are time-saving because of more narrow emission spectra. They are more convenient to use when treating larger areas because it is possible to use multiple lamps simultaneously. They are also inexpensive and easy to handle.

Different wavelengths can be used depending on the desired penetration depth.

The PpIX absorption curve is shown in fig. 3. The depths achieved with the different wavelengths and the advantages of each are as follows:

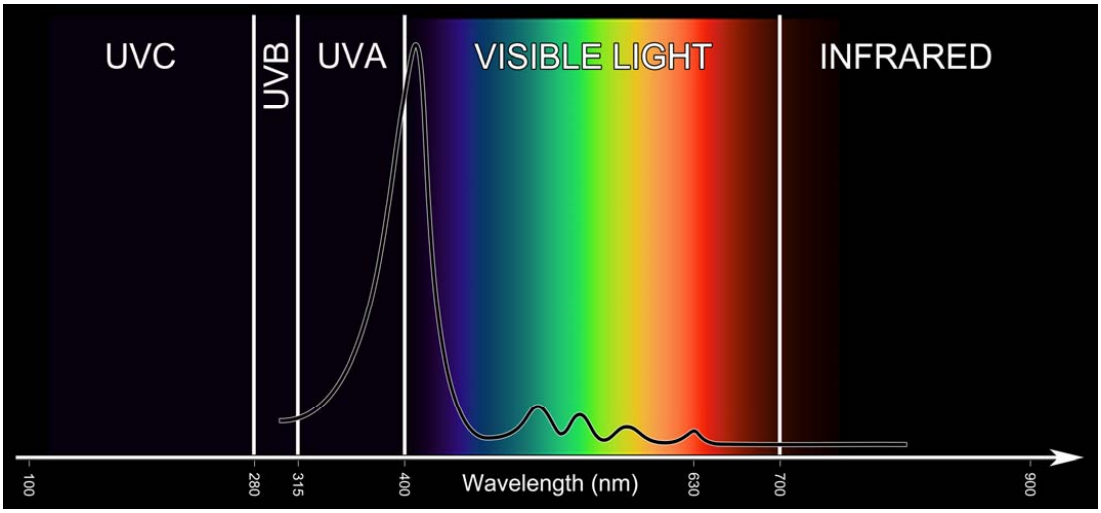


Figure 4. PpIX Absorption curve (Figure: Martin Gillstedt)

Red light (635 nm)

This is commonly used in Europe, and there are advantages with using red light. The penetration depth is up to 5 mm, allowing less superficial lesions to be treated.

Blue light (405 nm)

In the USA, blue light is preferred. Blue light has higher absorption of PpIX but less penetration depth in epidermal tissue (1 mm). Consequently this regimen is only suitable for very superficial lesions. Blue light can also be used for cosmetic purposes such as skin rejuvenation.[42]

Ambulatory low-irradiance organic light-emitting diode light (620 nm)

When this ambulatory device was applied for 3 hours the total dose delivered was 40–60 joule (J)/cm^2 with a fluence rate of 5 mW/cm^2.[43] The device consists of small lamps that have an area-emitting light source of 2 cm diameter, which may give the patient the possibility to perform the illumination in their home environment in the future.

Halogen lamp emitting visible light combined with water-filtered infrared A light

Another light source is the halogen lamp emitting VIS plus a water-filtered infrared A light (wIRA) (580-1,400 nm). Compared with LED lamps, using the VIS-wIRA combination is more suitable when no additional use of water spray is allowed during PDT.[44]

Daylight

Daylight can also be used as a light source when performing PDT of AKs. The photosensitizer (MAL) is applied to the skin and is continuously activated by daylight.[45] Daylight-mediated PDT achieves the same result but causes less pain compared with conventional PDT.

Coherent light

Lasers can be used as light sources. They are most commonly used when performing PDT with fibre optics in treatment of internal organs.[34] The advantages are the exact wavelength but the disadvantages using lasers are that only a small area can be treated at once and the device is expensive.

1.5 Side effects of photodynamic therapy

In general the PDT treatment is well tolerated. Side effects such as erythema, scaling and crusts are normal after treatment.[46] Oedema, in particular when areas around the eyes are treated, may also develop. The healing process is normally completed within 1–2 weeks but may take up to 6 weeks.[47] Our clinical experience has shown that hyperpigmentation can occur after PDT, especially when treating patients with skin type IV, but is usually resolved in a few months. Hypopigmentation can also be seen as a result of a debulking procedure.

The most problematic side effect is pain, both during treatment and sometimes for several hours after the treatment.

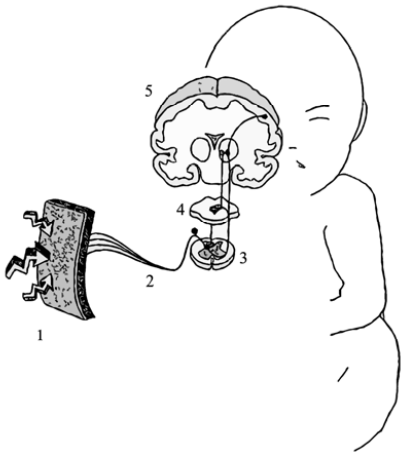
1.5.1 Pain

Pain has been defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Or in more simple words, pain is what the patient says hurts”. [48]

The pain experience can briefly be described as a sensory component mediated by the nociceptive system, and an emotional part that is mediated by the complex network in the cerebrum. Nociceptors are activated by imminent or existing tissue damage and signals are passed through the nerve fibres into the dorsal horn of the spinal cord. From the dorsal horn, the signals are passed via the reverse side of the ascending spinothalamic tract to the central switching station, the thalamus. From the thalamus, signals travel to the subcortical structures, including the basal ganglia and the limbic system, which is considered to be responsible for the emotional affective

component of the pain sensation. Impact of the hypothalamic areas initiates autonomic neuroendocrine stress responses, resulting in vegetative reactions such as nausea, hyperventilation, hypertension and tachycardia. The signals are finally projected to the cortical areas that are traditionally considered to be responsible for the conscious sensory discriminative component of pain.[49]

Figure 5. Pain pathways from:
1. nociceptors in peripheral tissue
2 .peripheral nerve fibres
3 .dorsal horn of the spinal cord
4. connection to the brain stem
5. to the thalamus and cortex



(Figure from the book “Smärta och smärtbehandling” with permission from the author)

Pain condition can be classified into time sequence, disease history and causal mechanisms.[50]

Acute and chronic pain

Pain is defined as “acute” or “chronic” depending on pain duration. If the pain remains after 3 months, it is classified as “chronic pain”. Acute pain often has an identifiable cause and it is possible to make a prognosis. By contrast, chronic pain may have a more unclear origin and the prognosis is more difficult to make. Pain relief in acute pain is often achieved with only analgesics. In chronic pain a

multidisciplinary treatment is often necessary. Pain relief is the primary goal but improved mobility and good quality of life are also of great importance.

Malignant or non-malignant pain

Cancer-related pain is usually more complex to treat for reasons related to existential, affective and cognitive components. Collaboration between various professional groups and physicians from different specialties may be appropriate. Depending on the progression of disease these painful conditions often change over time in character, intensity and location. Non-malignant pain is usually easier to treat but if the pain is chronic in nature, multidisciplinary treatment may be necessary.

Nociceptive pain, neuropathic pain and pain of unknown origin

Nociceptive pain occurs from imminent or existing tissue damage and is due to activation of pain receptors, nociceptors.

Neuropathic pain occurs due to pathological nerve impulses after an injury or a disease, e.g. stroke. The neuropathic pain can be divided in to central or peripheral neuropathic pain due to the pains origin.

Pain of unknown origin. This group includes pain that has not been classified as either nociceptive or neuropathic.[51] Previously this type of pain was referred to as "psychogenic pain". This is extremely rare, though psychological factors may have a great impact, especially in chronic pain.

1.5.2 Pain associated with photodynamic therapy

The intensity of the pain experienced varies between individuals, and is also dependent on the size of the treated area, as well as the diagnosis and location.[52, 53] When extensive AKs located on the forehead and scalp (field cancerization) are being treated, it is very common for the patient to experience severe pain. Patients have described this as “an uncommon burning, stinging pain”. The time of illumination is usually 8-10 minutes. The pain begins early during the illumination and peaks after the first minutes of treatment, where after it gradually decreases. After the illumination is completed the pain usually decreases over the next few hours, but in some cases it can persist for more than 24 hours.[38]

The mechanism of the pain associated with PDT is unknown but some theories have been presented. These include:

- Stimulation or damage of the nociceptors in the epidermal nerve endings by hypoxia or by singlet oxygen produced during the irradiation.[54]
- Presence of inflammation mediators such as adenosine triphosphate (ATP) and bradykinin.
- Stimulation of the transient receptor potential cation channel subfamily V member 1 (TRPV1), also known as the “capsaicin receptor” or the “vanilloid receptor”. Stimulation of this receptor causes a lower temperature threshold which induces a burning, stinging pain at normal skin temperatures.[55]
- Another possible receptor involved in pain and pain relief by cooling is the transient receptor potential cation channel subfamily M member 8 (TRPM8) also known as the cold and menthol receptor. Membrane voltage might contribute to the fine turning of cold and heat sensitivity in sensory cells.[56]

1.5.3 Pain assessment

The visual analogue scale

The most commonly used scale for pain assessment is the visual analogue scale (VAS). In the United States during the 1920s a method for measuring a subjective phenomenon was described, which can be viewed as a precursor of the VAS. It was called a “graphic rating scale (GRS)” and was used by raters to evaluate some personal aspects such as self-consciousness in individuals.[57] From the 1960s the VAS began to appear more frequently in the literature.

The VAS is a ruler with a 10 cm line on one side labelled “no pain” at one end and “unbearable pain” at the other. It has a numerical scale ranging from 0 (“no pain”) to 10 (“unbearable pain”) on the reverse side. (Fig. 6)

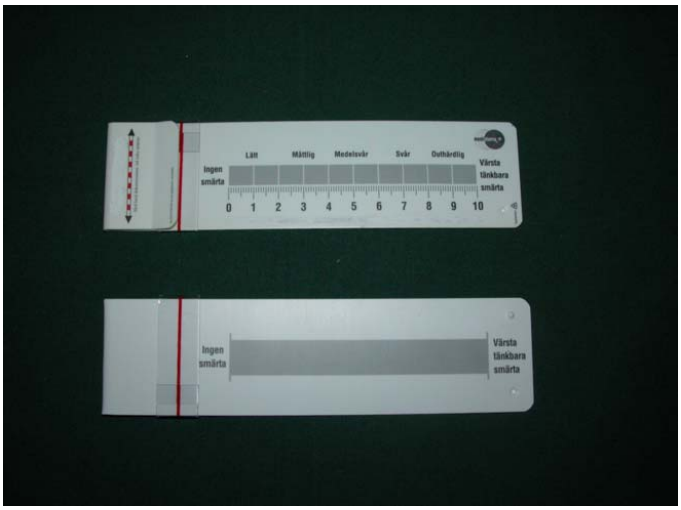


Figure 6. Visual Analogue Scale (Photo: Christina Halldin)

Critics of the instrument argue that it is a too simple and mechanical a way to measure a subjective phenomenon such as pain.[58] There is an ongoing debate

regarding VAS values, and whether they should be treated parametrically[59] or non-parametrically.[60, 61] The VAS was the most commonly used pain assessment method in our research studies (Papers II and III).

Numeric rating scale

The use of the numeric rating scale (NRS) is another option. It is used in a similar way as the VAS. Patients rate their pain numerically, with 0 corresponding to "no pain" and 10 to "unbearable pain".[62] This scale is most commonly used in clinical practice at our PDT unit (Paper I).

Verbal rating scale

The verbal rating scale (VRS) is an alternative instrument, on which patients assess the pain experienced with words instead of numbers. The five assessment alternatives are no pain (0), and mild (1), moderate (2), severe (3) and worst possible pain (4). The VRS is used by patients who find it difficult to use the VAS or NRS.[63]

1.5.4 Phenomenography

Another way to assess patients' pain experiences is to use a qualitative research approach. Phenomenography has potential, particularly when the objective is to find out about a patient's understanding of their experiences of a specific phenomenon.[64] Phenomenographic research comes from second-order perspectives as it describes how different aspects of reality are experienced by people. Individuals experience and understand different phenomena and aspects in the world around them in qualitatively different ways.[65, 66] The phenomenon under investigation in Paper IV is

the patients' experiences of PDT. Using individual interviews, we captured the patients' conceptions of being treated with PDT. We wanted to find as many different experiences of PDT as possible and consequently selected the patients to reflect various experiences of the same phenomenon.[67]

1.6 Modifiable factors prior to photodynamic therapy

1.6.1 Adequate information

One of the most basic and important actions before starting the PDT is to ensure that the patient has received adequate information about the various phases of the treatment. This information is usually presented to the patient when the treatment decision is taken, and it should include written information. Contact information should also be included in case questions arise after the visit to the hospital. Proper information about how the treatment is progressing can help patients to understand the treatment process and consequently feel more relaxed. One great challenge is to prevent miscommunication. The staff of the hospital may think that the information has been given very clearly; however, after the treatment the patient may ask questions that reveal that they have not understood the given information.

1.6.2 Photosensitization aminolaevulinic acid or methyl aminolaevulinate

There are different opinions about whether the choice of photosensitizer can influence the pain experience. Some studies have found MAL PDT to be less painful; [68-72] by contrast, other studies have found that there is no statistical difference in pain experience using ALA or MAL PDT.[73-75] Confounding factors may be different study protocols, e.g. concerning application time for the photosensitizer.

1.6.3 Light sources

Different light sources can have different influence on the pain experience.

A study by Babilas *et al.* showed that variable pulse light (VPL) laser could be less painful in treating AKs than the use of LED lamps.[76] Von Felbert *et al.* investigated different light sources using a halogen lamp emitting VIS combined with wIRA,

compared with the use of LEDs when performing MAL PDT of AKs.[44] They found an advantage to using VIS+wIRA compared with LEDs when no additional use of water spray was allowed during PDT. The most commonly used light source in PDT in Sweden is the LED lamp. Another method of reducing pain is to use an ambulatory low-irradiance organic LED light source.[43] Also, the use of daylight as light source has shown less pain during treatment.[45]

1.6.4 Fluence rate

Several studies have investigated the effect on pain by using different fluence rates during PDT.[77-81] These studies indicate that a lower fluence rate is less painful for the patients without interfering with the cure rates. Fractionated illumination has been investigated showing better clinical response but without effect of pain relief.[82] Further investigations are needed to optimize the PDT protocol for different indications and photosensitizers.

1.7 Pain-relieving methods

1.7.1 Friendly atmosphere and distraction

Our clinical experience is that a friendly atmosphere can make a considerable difference. The staff can chat with the patient or offer the patient the possibility to listen to music during treatment. This can create some distraction and the feeling of the treatment being brief.

1.7.2 Water spray, pauses and cold air analgesia

Spraying cold water over the treated area in combination with pauses when needed is a common pain-relieving method. A study by Wiegell *et al.* showed that water

spray or using cool packs resulted in a minor reduction of the pain but if a (3-minute) pause was added the pain was considerably reduced.[83] Studies have investigated pain relief by cold air and a comparison with NBs has also been conducted.[84, 85] Cold air analgesia showed a significant pain-relieving effect only after the second PDT session. The result of the comparison between cold air analgesia and NBs was in favour of NBs. During illumination, the sensitizer is photo-oxidized, in a photobleaching process that is oxygen-dependent. The rate of photobleaching will be dependent on the availability of molecular oxygen.[78] This means that there may be a risk of a decreased level of molecular oxygen if the blood perfusion is reduced in the skin due to a decrease in temperature with the cooling.

In a recent study by Tyrrell *et al.* it was shown that the use of air cooling as pain relief resulted in lower PpIX photobleaching and consequently a reduction in efficacy.[86] A different approach regarding the use of cool air is shown by Stangeland and Kroon.[87] In their study the skin temperature during PDT was higher than in the study by Tyrrell and consequently a better treatment outcome was achieved.

1.7.3 Topical anaesthetics

Several studies have investigated the use of topical anaesthetics as pain relief, such as tetracaine gel, morphine gel and lidocaine–prilocain gel, without adequate effect.[88-90]

1.7.4 Local-infiltration anaesthesia

When a more invasive curettage is performed prior to MAL application or in small painful lesions, local-infiltration anaesthesia (LIA) may be useful.

1.7.5 Subcutaneous infiltration anaesthesia

Borelli *et al* used subcutaneous infiltration anaesthesia (SIA) as pain relief during PDT of AKs on the cheeks.[91] The local anaesthetics were diluted in Ringer's solution, injected slowly using an injection pump. The patients received 40–60 ml of the solution. The pain-relieving effect was adequate with SIA; however, one disadvantage was the oedema on the treated area days after the treatment. In extensive areas of AKs, such as field cancerization on the forehead and scalp, this method is not appropriate.

1.7.6 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation can be used as pain relief in acute and chronic pain, e.g. postoperative pain, angina pectoris, labour pain and chronic lower back pain.[92-97] The mechanism behind TENS is based on the gate control theory.[98, 99] This theory is based on a gate control mechanism, which exists in the dorsal horn of the spinal cord. Signals through large-diameter nerve fibres (Aβ fibres) are said to inhibit the central transmission of signals through small-diameter nerve fibres (Aδ and C fibres), "closing the gate". Since Aβ fibres have a low threshold for electrical stimulation, they can be activated through stimulation with electrodes, which is used in TENS. Despite the fact that the gate control theory has received much criticism and is today not accepted in its original presentation, the theory has had great impact in different pain treatment modalities such as TENS and spinal cord stimulation. Studies have been investigating TENS for other indications such as procedural pain, with varying results.[100, 101] Since new pain-relieving strategies for PDT are required, TENS is an interesting alternative.

1.7.7 Nerve blocks

The use of NBs during surgical procedures on the head and neck area is common.[102-105] An alternative for pain relief associated with PDT of the forehead and scalp is to perform different NBs. With combinations of supra- and infraorbital, supratrochlear and mental NBs the whole main area of the face can be anaesthetized.[106] Nerve blocks of the greater and lesser occipital nerves can also be used to achieve anaesthesia for the scalp. Dorsal penile NBs used as pain relief have been reported elsewhere.[107]

Side effects associated with NBs are rare but may occur. Regarding nerve blocks of the face, it can be difficult to eat and chew when the lips are anaesthetized. This may result in damage to the lips or mouth of the patient. A NB of the supraorbital nerve that is given too low may result in a transient ptosis.

1.7.8 Spinal anaesthesia and general anaesthesia

In some unusual conditions, such as Paget's disease in the genital area, there is a need for a more powerful anaesthesia such as spinal anaesthesia. General anaesthesia could be an alternative, in particular when performing PDT on large numbers of BCCs e.g. in Gorlin's syndrome in extensive areas on one occasion. After PDT, the patient remains in the hospital overnight. Instead of many potentially painful PDT treatments and several healing periods, the areas are treated simultaneously, resulting in only one healing period.

2. AIMS OF THE INVESTIGATION

The overall aim of this thesis was to investigate and identify factors of pain associated with PDT, and try to achieve effective methods to reduce the pain during treatment. The aims of the investigations carried out as part of this thesis were:

Paper I

- to investigate and identify predictors of pain associated with PDT

Paper II

- to investigate and evaluate TENS as a pain-relieving method during PDT of AKs in the face and/or scalp

Paper III

- to investigate whether the combination of occipital and frontal NBs will provide adequate pain relief during PDT of field cancerization of the forehead and scalp

Paper IV

- to explore and describe the patients' experiences of PDT

3. PATIENTS AND METHODS

3.1 Paper I

3.1.1 Patients

Our patient population receiving PDT during 2004 consisted of 52% men and 48% women (Paper I). Most of the patients treated with PDT for extensive AKs in the face and scalp were men. The explanation for this is gender-linked, since hair thinning and baldness are more common in men (Papers II-IV).

All patients treated with PDT at our unit during 2004 were included in the study, giving a total number of 377 patients (197 men and 180 women). The mean age of the men was 72 years (range 18-93 years) and of the women 71 years (range 32-92 years). During 2004, 658 PDT sessions were conducted, with altogether 1,155 treatment fields, a treatment field being the area covered by a single PDT lamp. The study design was a descriptive, retrospective study and the patients' data records were used to assess the clinical data.

3.1.2 Methods

Pain evaluation

To assess the pain experienced by the patients, a VAS or NRS was used. In clinical practice during 2004, the NRS was used most often.

In this retrospective study, VAS or NRS scores were not always obtained for each treatment field but more often for a group of treatment fields defined as a "treatment area". In more than half of the patients (58%), more than one PDT treatment area was assessed using a VAS or NRS. However, each separate VAS or NRS score was included in the analysis.

Pain-relieving methods

Before PDT, oral and written information about the procedure was given. Use of cold water spray and pauses, in combination with distracting conversation, was the standard pain-relieving routine during PDT.

When severe pain occurred or was predicted, pain relief such as infiltration anaesthesia and NBs (genital area) was used. On rare occasions, spinal or general anaesthesia was administered.

Diagnoses

Actinic keratoses were present in 229 patients, BCCs in 128 patients and SCC in situ in 35 patients. Some patients had a combination of diagnoses (e.g. AKs and BCCs at the extremities). Other diagnoses (e.g. Paget's disease and lichen sclerosus) were present in 20 patients also treated with PDT.

Lesion location

The patients' lesions were divided into four separate body areas regarding the location of the lesions. The body areas were face and/or scalp, the trunk, the upper extremities, and the lower extremities.

Size of treatment field

In this study, two different sizes of irradiation lamps (Aktilite CL 128 and Aktilite CL 16; Photocure ASA, Oslo, Norway) were used when performing PDT, the Aktilite CL 128 (large lamp) with a maximal irradiation area of 8 x 18 cm and the Aktilite CL 16

(small lamp) with an irradiation area of 4 x 5 cm. When large areas were treated, several Aktilite lamps were used simultaneously.

Routine preparation of lesions

The treatment field or area was prepared according to our hospital routine. A light curettage with no bleeding was performed on the lesions before MAL cream 160 mg/g (Metvix®; Photocure ASA, Oslo, Norway) was applied on the treatment area. The MAL cream was administered on the lesions in an approximately 1 mm thick layer with a surrounding area of at least 1 cm^2. Occlusive dressings (Tegaderm™; 3M Health Care, Neuss, Germany, and Mefix®, Mölnlycke Health Care AB, Gothenburg, Sweden) were used to cover the treatment area. After 3 hours, the cream was gently removed.

Nodular lesion preparation

In 20 nodular BCCs, perforation was performed prior to PDT because it was thought to increase penetration of the photosensitizer in these lesions. Eleven other nodular BCCs were also included, but because of their thickness these were more extensively curettaged prior to PDT.

Photodynamic therapy irradiation

Irradiation was performed using visible red light from LED lamps (Aktilite® CL 128 and/or CL 16 lamps; Photocure ASA, Oslo, Norway) with a mean wavelength of 635 nm. The fluence rate was 80–90 mW/cm^2 and irradiation was given for 8-10 minutes, resulting in a total light dose of 37–45 J/cm^2.

The standard hospital routine (two PDT sessions with an interval of 1–2 weeks) for the treatment of BCC and SCC in situ was used.

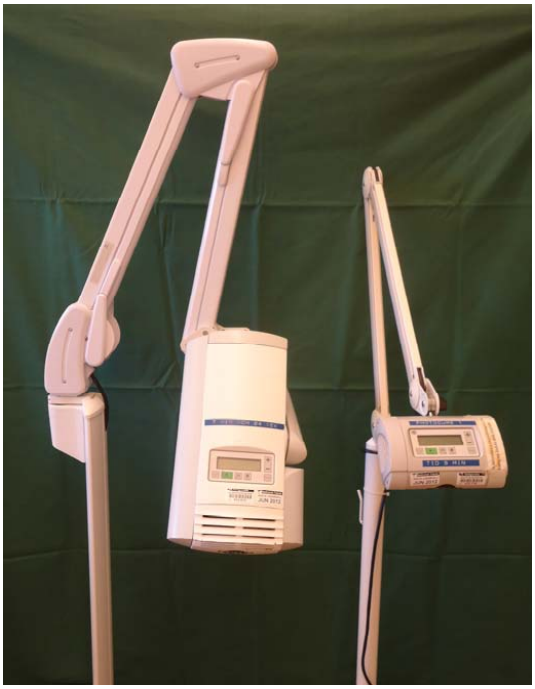


Figure 7. LED lamp Aktilite® CL 128 and CL 16 (Photo: Christina Halldin)

Follow-up

The follow-up time varied between 3 months and 3 years depending on the diagnosis. Patients with AKs had individualized follow-up visits.

3.2 Paper II

3.2.1 Patients

In this pilot study, 14 male patients with a mean age of 75 years (range 46-86 years) were included. They had AKs on the face and scalp and previous experience of severe pain during PDT sessions.

3.2.2 Methods

Transcutaneous electrical nerve stimulation

The two TENS electrodes (Cefar originale electrodes, size 5 x 10 cm; Cefar Medical AB, Malmö, Sweden) were placed on the patient's shoulders. The skin was washed with soap and water and dried off to obtain good contact between the electrodes and the patient's skin. We chose to place the electrodes on the shoulders to avoid contact with areas treated with PDT and allow the use of regular pain-relieving methods such as water spray. The electrodes were connected to a control unit (Cefar primo; Cefar Medical AB, Malmö, Sweden). A high-frequency modulated pulse rate of 80 Hz was used to give an undulating sensation, which may be more pleasant than constant pulse duration, according to the recommendation of the manufacturer. The pulse duration varied from 70 to 180 μs and back within 2 seconds, and the pattern was repeated. The intensity of the stimulation could be changed by varying the current from 0.5 to 60 mA in steps of 0.5 mA. The stimulation started about 20 minutes (range 10-25 minutes) before PDT.

During treatment the strength of the stimulation was controlled by the patient, if required with support from the study nurse.

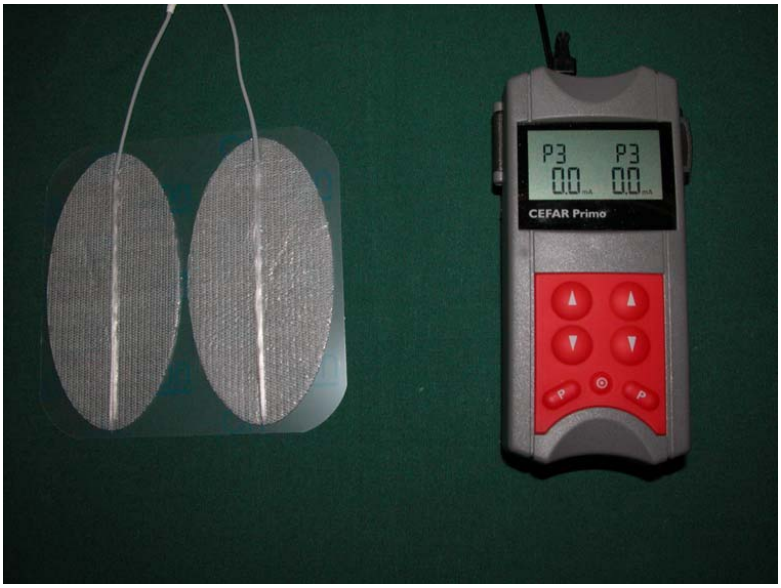


Figure 8. TENS unit and electrodes (Photo: Christina Halldin)

The maximum level of the TENS stimulation applied in all patients was on average 36±4.2 mA (range 17-60 mA).

After completing PDT, the TENS stimulation continued for approximately 8 minutes (range 3-17 minutes).

Photodynamic therapy procedure

The AKs were prepared according to our hospital routine with light curettage before application of the MAL cream under occlusion for 3 hours. The treatment areas were

irradiated with red light (634 nm, fluence rate of 80-90 mW/cm^2, and a total light dose of 37-45 J/cm^2) using a LED lamp.

Pain evaluation

The pain perceived by the patients was assessed using a VAS. Patients were asked to assess the maximum pain experienced during treatment, immediately after treatment and 15 minutes after completion of treatment. To obtain an assessment for how the patients experienced the TENS procedure and the pain-relieving effect, a short questionnaire was answered after completion of PDT with TENS and at the follow-up visit after 2 months.

Follow-up

The patients returned to the clinic for a follow-up visit after 2 months for examination of the clinical outcome of PDT.

3.3 Paper III

3.3.1 Patients

Ten men with a mean age of 76 years (range 70-84 years) and with symmetrically distributed, extensive AKs were included in the study. They all had signs of field cancerization on the face and/or scalp.

3.3.2 Methods

Nerve blocks

In this study, the NBs were performed on one side of the forehead and/or scalp while the other side served as the patient's own control. Nerve blocks were applied at least 15 minutes before PDT irradiation in order to ensure good distribution of the half-sided local anaesthetic. Before the NB was performed the injection area was cleaned with an antiseptic agent. The needle was inserted until bone contact and then slightly withdrawn. To ensure the needle was not in a blood vessel, aspiration was done and then the local anaesthetic was slowly injected. After randomization with regard to the side to be anaesthetized, the NBs were applied unilaterally in the occipital and frontal area. The local anaesthetic bupivacaine (Marcaine®-adrenaline 5 mg/ml and 5µg/ml; AstraZeneca AB, Södertälje, Sweden) was used for the NBs. Duration of the anaesthesia was 4-6 hours. The irradiation was conducted simultaneously on the anaesthetized and non-anaesthetized treatment areas.

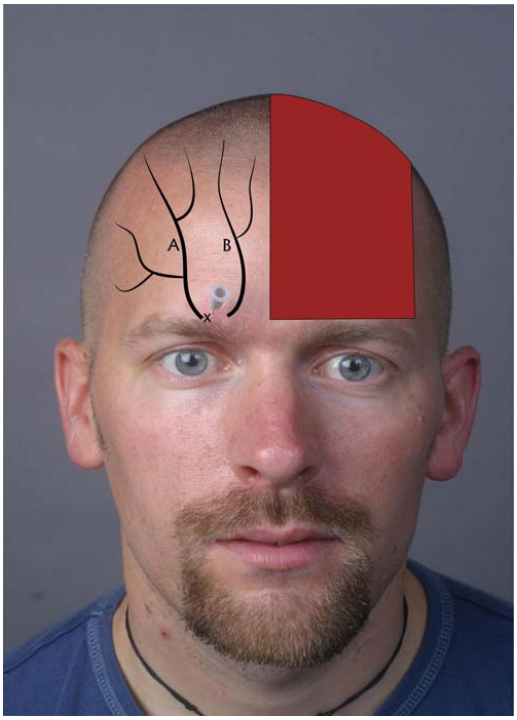


Figure 9. The distribution of the supraorbital (A) and supratrochlear (B) nerves and injection site for the frontal nerve blocks slightly above the supraorbital foramen (X). The corresponding area of cutaneous anaesthesia is marked with red.

(Informed consent obtained, photo: Morgan Carlsson)

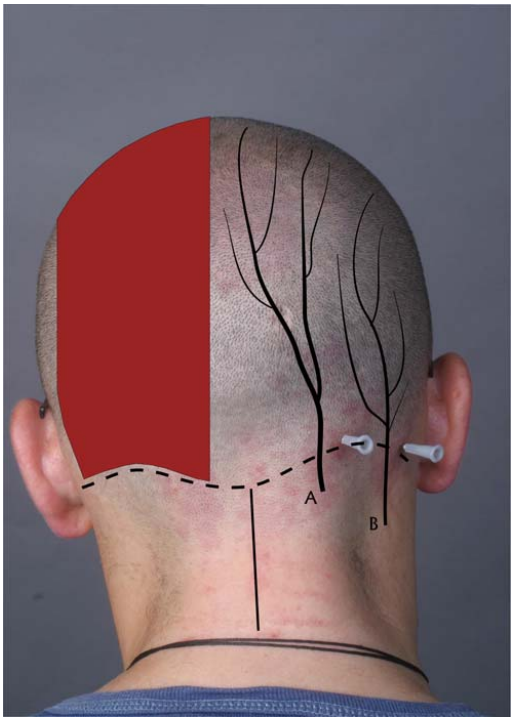


Figure 10. The distribution of the greater (A) and lesser (B) occipital nerves and the injection site for the respective nerve blocks along the superior nuchal line (dotted line). The corresponding area of cutaneous anaesthesia is marked with red.

Skin preparation

The AKs were prepared according to our hospital routines with light curettage before application of the MAL cream under occlusion for 3 hours.

Irradiation

The treatment areas were irradiated with red light (634 nm, fluence rate 80-90 m W/cm^2, and a total light dose of 37-45 J/cm^2) using an LED lamp as previously.

Pain evaluation

The maximum pain perceived by the patient was assessed using a VAS. Each treated side was assessed separately and the side with no NB served as the patient's own control.

Follow-up

The patients were contacted by telephone within 2 weeks of the treatment to assess the pain experienced during the hours after PDT and to record any adverse event. Patients returned to the clinic for a follow-up visit after 8-14 weeks for examination of the clinical outcome of PDT.

3.4 Paper IV

3.4.1 Patients

In this qualitative study 18 patients were interviewed. They were 14 men and four women, reflecting the normal patient population with pre-cancerous lesions in the face or scalp at our clinic. The average age of the men was 79 years (range 65-87 years) and of the women, 68 years (range 49-78 years).

3.4.2 Methods

Phenomenography

In this study, phenomenography as a qualitative research approach was used.

Data collection

Semi-structured interviews were performed individually. The main open-ended interview question was, “Could you please tell me about your experience of PDT?” The patient decided where the interview should take place, e.g. in the researcher’s office at the hospital or another place of the patient’s choice. Patients described their experiences of being treated with PDT with their own words. The interviews were tape-recorded and transcribed verbatim.

Data analysis

The data were analysed according to the principles of phenomenography, as described by Alexandersson.[108] The process can be divided into four phases:

- Becoming familiar with and gaining an overall impression of the data
- Noting similarities and differences in statements
- Determining descriptive categories of conceptions
- Examining the underlying structure of the system of categorization

Categories of description were formed, which cover statements related to the patients' experiences of PDT.

Credibility

In qualitative research the results should be presented as an inner logic. This means that the reader should have the possibility to follow the researcher's logic throughout the study. Credibility is a question of how well the categories represent the patients' conceptions and are not simply a construction of the researcher.[109] The quotations should give the reader an opportunity to evaluate the credibility of the researcher's analysis. A co-examiner was assigned by the researcher to test the credibility of the categories. This was done in a reverse order, with the co-examiner investigating whether the categories are consistent with the quotations from the interviews. Almost total coherence existed from the beginning between the evaluation of the researcher and the co-examiner's evaluation.

3.5 Statistical methods

3.5.1 Paper I

All data were analysed using R version 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria). A mixed-effect logistic regression model for a dichotomous pain response was used (VAS ≤5 v. >5). The size of the irradiation field (small v. large), the diagnosis (BCC v. AK) and lesion location (face and/or scalp v. trunk or extremities) were used as fixed effects.

Wilcoxon-Mann-Whitney's test was used for pair-wise comparisons of VAS scores between groups. Bonferroni correction was used to adjust the significance level for multiple pair-wise comparisons. The follow-up visits of patients treated for BCCs were analysed using survival analysis for interval-censored data. An exact log-rank test (permutation form) was carried out to compare clearance rates for nodular and superficial BCCs.

3.5.2 Paper II

The differences between baseline VAS scores and assessment obtained during PDT with TENS were analysed using a paired *t*-test (Microsoft Excel; Microsoft, Seattle, WA, USA). Error limits reported represent standard error of the mean (SEM). Statistical significance was set to $p<0.05$.

3.5.3 Paper III

From our clinical experience we know that the VAS scores are between 5 and 10 when treating AKs on the face and scalp without anaesthesia. In the power analysis, the assumption was made that the patients had a mean VAS score of 7.5 with a

standard deviation (SD) of 2 on the non-anaesthetized side. On the NB side we assumed the VAS score to decrease by 5. To detect a power of 99%, a sample size of ten patients was required to show this difference. A paired *t*-test (Microsoft Excel; Microsoft, Seattle, WA, USA) was used to compare the mean scores. Error limits reported represent SEM. Statistical significance was set to $p<0.05$.

3.6 Qualitative method

3.6.1 Paper IV

In this study, phenomenography as a qualitative research approach was used. Individual interviews were conducted with 18 patients and the transcribed verbatim interviews were used as data and analysed using a phenomenographic approach.

3.7 Ethics

3.7.1 Paper I

Ethical approval was not considered necessary by the regional Ethics Committee in Gothenburg, Sweden.

3.7.2 Papers II–IV

The studies were approved by the regional Ethics Committee in Gothenburg, Sweden.

4. RESULTS

4.1 Paper I

4.1.1 Diagnoses

The most commonly treated diagnosis was AK (*n*=229) with mean VAS scores of 6.1±0.14, compared with mean VAS scores of 4.6±0.15 for patients with BCCs (*n*=128). Squamous cell carcinoma in situ (*n*=35) was also less painful to treat compared with AKs, with a mean VAS score of 5.0±0.34.

4.1.2 Lesion location

Photodynamic therapy performed on the face and/or scalp was more painful than treatment on other body locations ($p<0.05$). Photodynamic therapy of AKs on large areas of the forehead and scalp was particularly painful (mean VAS 6.7±0.17).

4.1.3 Size of treated area

The size of the treated area was a good predictor and had the strongest statistical significance ($p<0.0001$). Compared with diagnosis and location, treating a larger area (one to four lamps for an area of 144-576 cm^2) was more painful.

4.1.4 Gender and age

There were no statistical differences in pain experience between men and women. Men over the age of 70 years with AKs in the face and scalp scored the pain experienced higher than younger men. However, this trend was not considered relevant, since elderly men were often treated for extensive AKs (field cancerization), whereas younger men received PDT on smaller treatment areas.

4.1.5 Comparison between groups

The patients' data were divided into eight groups according to diagnosis, location and size of the treated area. Larger areas were significantly more painful compared with smaller areas. When comparing locations, AKs in the facial area were significantly more painful than on the trunk or extremities regardless of the size of the treated area.

4.1.6 Pain-relieving methods

The most common way to cope with the pain during treatment was use of cold water spray. Local-infiltration anaesthesia was used when severe pain occurred during treatment or during painful pre-treatment, such as extensive curettage or perforation of nodular BCCs, before application of the photosensitizer.

4.1.7 Follow-up and clinical outcome

In this retrospective study the treatment outcome was not the primary objective, although 95 out of 127 superficial BCCs were followed for 3 years. A complete clearance was seen in 62% of these lesions. Patients with 32 BCCs were either lost to follow-up or further controls were not considered necessary. The perforation of the nodular BCCs did not lead to better clinical outcome: after 3 years only six out of 19 lesions (32%) remained cleared without recurrence.

4.2 Paper II

The patients' average VAS values from previous PDT sessions in the same area were used as baseline value. The difference between the baseline VAS score (±SEM) and the assessments obtained during PDT with TENS was compared. The mean VAS score was 8.1 (±0.3) without TENS and 6.2 (±0.4) with TENS in association with PDT. The differences in VAS scores obtained are shown in Figure 1, Paper II (p. 311). All patients were able to complete PDT when TENS was used; previously, three out of 14 patients (21%) had disrupted the treatment owing to unbearable pain. In four patients, TENS during treatment had no effect.

4.2.1 Follow-up and clinical outcome

The patients completed a short questionnaire about their experiences using TENS. This was done directly after the PDT treatment and at the follow-up visit. The result of the questionnaire showed that TENS was easy to use and 13 out of 14 patients said they would like to use it again if PDT was required in the future. Two patients experienced a mild, easily tolerated ache of the shoulder muscles the day after the treatment, but this had resolved within 1 day. At the follow-up visit the cure rate was 80-100% after one PDT session.

4.3 Paper III

4.3.1 Pain evaluation

On the anaesthetized side the patients had a mean VAS score of 1±0.29 compared with VAS 6.4±0.82 on the non-anaesthetized side. One patient could not complete the treatment because of unbearable pain on the non-anaesthetized side.

4.3.2 Follow-up

The patients were followed up by telephone within 2 weeks of the treatment. When the effect of the NB had worn off, nine out of ten patients had experienced no remaining pain. No adverse events had occurred as a result of the NBs.

4.3.3 Clinical outcome

The patients showed a clearance rate of >75% after PDT. No difference in cure rate was observed between the anaesthetized and non-anaesthetized sides after 8-14 weeks at the follow-up visit. One patient with extensive and thick AKs had been prescribed two treatments in advance, the other patients only received one treatment.

4.4 Paper IV

In this interview study, the patients' statements were divided into three themes, with ten accompanying categories. Quotes from the interviews are used to describe the patients' varying experiences of events associated with PDT.

4.4.1 Theme 1: Treatment without nerve blocks

This theme contains statements of the patients' experience of PDT without anaesthesia. The categories were: "Burning, stinging pain", "Getting professional help to ease the pain", "Finding personal strategies to ease the pain" and "It was worth the pain".

4.4.2 Theme 2: Treatment with nerve blocks

In this theme the patients describe their experiences of being treated with NBs for anaesthesia during PDT. The following categories emerged: "Feeling the sting of the injections", "Pain relief" and "Prolonged effect".

4.4.3 Theme 3: Feeling the effects of the treatment on the skin

The need to express their feeling of the effects on the skin after PDT was not expressed by all patients. However, those patients who decided to describe their feelings regarding the effect of PDT had had strong effects on the skin after treatment. The following categories relate to the patients' experiences: "Redness, crusts and scaling", "Anxiety when looking at the skin" and "The feeling of a healthy skin".

5. DISCUSSION

5.1 Paper I

5.1.1 Methodological considerations

This study was a descriptive retrospective study whose primary objective was to identify predictors of pain. The secondary objective was to investigate how many patients treated with PDT experienced pain. A mixed-effects logistic regression was used because one patient could have multiple measurements, which therefore could not be regarded as independent. Logistic regression was used on the dichotomized pain, i.e. VAS ≤5 v. VAS >5, to avoid a normality assumption for the VAS values. Despite the fact that it then becomes a more conservative test the predictors were still significant.

In retrospect it may have been better to perform a prospective study to identify pain predictors. However, this design describes our clinical reality.

5.1.2 General discussion

During the years a number of studies have investigated the important issue of pain associated with PDT.[43-46, 52, 53, 68-75, 78-80, 83, 84, 88-91, 106, 110-112] Our results are consistent with studies performed by Grapengiesser *et al.* and Sandberg *et al.* [52, 53] which show that pain in PDT is not a severe problem for all patients although it is a considerable issue for some. The size of the treated area is the most crucial factor in pain experienced during PDT, followed by diagnosis and location. Grapengiesser *et al.* [52] found that men had more pain then women. In our study we did not find any differences regarding gender. In this retrospective study fluorescence and skin-types were not investigated since these data were not available in all patients.

5.2 Paper II

5.2.1 Methodological considerations

This study was a pilot study investigating whether TENS could give some pain relief during PDT. In retrospect it would have been more adequate to use a "split-head" design to compare with instead of using the patients' previous VAS values. In the statistical analysis, a non-parametric test such as Wilcoxon's signed rank test may have been a better choice, although this study did not show any major difference in results. The paired *t*-test showed a *p*-value of 0.0033 compared with *p*=0.0073 for the Wilcoxon signed rank test.

5.2.2 General discussion

Transcutaneous electrical nerve stimulation has been used in several other treatments as a method to achieve pain relief for procedural pain. One part of the pain-relieving effect of TENS is probably a distracting effect when the patient is concentrating on regulating the TENS unit during the treatment. Placing the electrodes closer to the treated area would likely have given more effective pain relief. Two patients experienced muscle soreness after TENS; this was possibly related to the TENS procedure. The 1.9 decrease in VAS score may seem minor but a study by Todd *et al.* found that changes in VAS score >1.3 could be of clinical importance.[113]

5.3 Paper III

5.3.1 Methodological considerations

In this study we used a split face/scalp design that allowed the patients to be their own control. Since the pain experienced during PDT is a subjective experience and there is great variability between patients, this design is preferable. The patients had no difficulty in assessing the pain on the different sides. It is not possible to find patients with exactly the same amount of AKs bilaterally but the patients were randomized with regard to the side to be anaesthetized.

5.3.2 General discussion

There is great benefit for patients in having the possibility to receive NBs as pain relief before PDT in the face/scalp area. The temples are an area that is usually not anaesthetized by blocking of the supraorbitalis and supratrochlearis nerves. There may be a possibility to perform NBs in the temple area but this has to be investigated further. In this study the local anaesthetic bupivacaine was used, giving 4-6 hours of anaesthesia. In some cases, e.g. where NBs were given as pain relief during PDT of actinic cheilitis, a shorter-lasting local anaesthetic may have been a better choice. This would have enabled the patients to eat sooner after treatment.

5.4 Paper IV

5.4.1 Methodological considerations

The selection of patients was based on gender, age and varying experience of being treated with PDT with and without pain relief. The patients' journals were read prior to the selection of patients for the study, in order to obtain a variation of experiences of being treated with PDT. A larger number of patients may have resulted in a greater variation of statements. However, the number (18 interviews) was considered realistic while using individual qualitative open-ended interviews.

Qualitative interviews are often semi-structured, which means that the same question is given to all interviewees, and the interviewer then probes further by asking supplementary questions, such as "Can you explain further?" Interviews are often conducted individually or in focus groups. The latter method involves interviewing a group of usually four to ten people. The reason why individual interviews were chosen in this study was that experience of pain could be a sensitive topic. Especially elderly men >70 years may have difficulty talking about feelings. In our clinical experience, we find that more men than women remain silent rather than reveal verbally that they have a difficult time with pain during treatment.[114]

5.4.2 General discussion

Several previous studies have investigated patients' experiences of pain and pain relief during PDT. [43-46, 52, 53, 68-75, 78-80, 83, 84, 88-91, 106, 110-112] The most common method is to assess the pain using a VAS. Another option is to use a qualitative approach as

a complement to statistical analysis. Phenomenography could be used to capture the patients' different experiences of being treated with PDT. The individual interviews were conducted to explore and describe the patients' experiences of PDT. To capture the patients' perspectives and gain an overall picture of their experiences of the treatment a phenomenographic approach was used. A patient's personal statements, in their own words, can highlight and add understanding of their experience at a deeper level. A different type of knowledge than provided by numbers on a VAS can be achieved with a phenomenographic approach. This qualitative knowledge adds to the understanding of being a patient in a specific context with specific treatments and highlights the patient's perspective. The patient's own words and experiences will be taken into consideration in further development of treatments.

6. SPECULATION REGARDING PAIN IN PHOTODYNAMIC THERAPY OF FIELD CANCERIZATION

It may be speculated whether the pain in a man with extensive AKs on the forehead and scalp could be influenced by different mechanisms which could contribute to the pain experienced during PDT.

- The face and scalp have dense innervation, hence it can be assumed that this area has many superficial epidermal nerve endings with nociceptors, which can be stimulated by the photodynamic process
- Stimulation of the TRPV1 creates a lower temperature threshold, which induces a burning, stinging pain at normal skin temperatures. In a study by Palson *et al.* superficial perfusion and temperature during PDT of BCCs using ALA and MAL was investigated. They showed only a small increase in temperature of 2.2ºC during PDT, which is well below the level of hyperthermia.[115] No difference in temperature was found between ALA and MAL PDT on the lesions
- The presence of inflammation mediators, such as ATP and bradykinin, could contribute to the pain experienced by activating TRPV1[116]
- There are signs that TPRV1 is present in the keratinocytes in the skin[117]

If TRPVT1 is present in both the epidermal nerve endings and in the keratinocytes, one way of solving the pain problem may be to use TPRVT1 inhibitors. Phase I/II clinical trials for TRPV1inhibitors/ antagonists are underway. [118] In a pilot study by Sandberg *et al.* capsaicin cream (agonist desensitization of TRPVT1) was used as pre-treatment 1 week prior to PDT.[53] No pain-relieving effect was found during treatment, but capsaicin may be of interest applied with another protocol.[119, 120]

7. CONCLUSIONS

7.1 Paper I

The size of the treatment area, the diagnosis and the location of the lesions are pain predictors to be taken into consideration when using PDT, in order to provide adequate information and pain management. However, there is large variance in VAS assessment within patients, consequently limiting the possibility to predict pain.

7.2 Paper II

The pain-relieving effect of TENS during PDT was limited, although the responses to the questionnaire imply that TENS is easy to use and was well accepted as pain relief by the patients. It is desirable to further improve the pain-relieving efficiency during PDT of AKs in the head region. Future studies are needed in this area. Hopefully, a more specific electrode placement around the treatment area may further improve the pain-relieving effect.

7.3 Paper III

The NBs achieved satisfactory pain relief for most of the patients receiving PDT of AKs on the forehead and scalp and no negative effect of the treatment outcome was seen. One limitation is that the temples are not completely covered by currently available NBs.

As a result of this study, NBs are now included in routine practice at our PDT unit at Sahlgrenska University Hospital.

7.4 Paper IV

The patients' conceptions showed coherence about the pain they experienced during PDT without anaesthesia. The pain was experienced as very intense but the result in the end "made it worth it". The patients said that NBs gave satisfactory pain relief. However, as NBs were experienced in different ways, the conclusion is that NBs are not appropriate for all individuals and that it is not possible to use them in certain body sites. Further research is needed to find alternative options for reducing pain.

8. OUTLOOK FOR THE FUTURE

The most troublesome side effect of PDT is pain, despite the fact that statements from patients led to the conclusion that it “was worth the pain”. It is desirable to find pain-relieving methods that are effective for all patients and treatment areas.

8.1 Transcutaneous electrical nerve stimulation

It would be interesting to investigate whether a more specific placement of the TENS electrodes could achieve better pain relief during PDT of AKS on the forehead and scalp. Transcutaneous electrical nerve stimulation is even possible to use as pain relief in other painful treatment areas such as the chest or the lower extremities.

8.2 Nerve blocks

The challenge remains to develop the technology to perform NBs in such a way as to complement our NB routine with anaesthesia of the nerves and thus achieve pain relief for the temple areas. Other treatment areas may also be suitable for periphery NBs, such as NBs of the hands.

8.3 Photodynamic therapy protocol

It should be investigated whether a change in the protocol for performing PDT would decrease the pain experienced by the patients. Studies have shown a decrease in pain intensity during PDT with lower irradiance, without reducing the cure rates.[77, 79, 81] These studies were performed with ALA PDT as photosensitizer and similar studies using MAL PDT may be interesting to perform. Wiegell *et al* have investigated PDT with lower irradiance using MAL but in this study patients with acne were

treated.[80] A study investigating the photosensitizers with similar application time for ALA and MAL may likewise be of interest.

8.4 TRPV1 inhibitors/antagonists

When there is a TRPV1 inhibitor/antagonist available it would be interesting to study if this substance will make any difference in the pain experienced by the patients being treated with PDT. Whether, the hypothesis is true about the involvement of the TRPV1 receptor in the stinging burning pain during PDT. A pretreatment before the PDT session may hopefully give some pain relief during treatment.

8.5 Indoor "daylight" mediated photodynamic therapy

One interesting thought would be to try to perform daylight mediated PDT indoors. This will be performed in a large room with white walls and with light sources on the ceiling; this should give a light dose equivalent to daylight outside. When using a room like this, there is no problem to perform daylight PDT in the wintertime or when it is raining heavily outside. In this room there will be comfortable chairs or beds for the patients to relax in and green plants and soft music to get a comfortable environment. In addition there will also be a possibility to have a cool drink or coffee or tea during the treatment. This indoor daylight mediated PDT could be of special interest for patients with extensive AKs as an alternative to conventional PDT.

9. SVENSK RESUMÉ

Fotodynamisk terapi- smärta och aspekter på smärtlindring.

Fotodynamisk terapi (PDT) används för att behandla aktiniska keratoser s.k. solskador (tidigt förstadium till skivepitelcancer) och vissa typer av icke melanom hudcancer. Nedan följer en kort beskrivning på svenska utan medicinska termer om hur det går till att behandla med PDT, därefter följer en genomgång av studierna som ingår i denna avhandling.

PDT-behandlingen har två delar, först prepareras huden och därefter belyses behandlingsområdet med rött synligt ljus.

- Det område på huden som skall behandlas skrapas lätt för att förtjockad hud skall lossna. Därefter stryks en kräm på området som innehåller ett ämne som gör tumörceller extra känsliga för synligt rött ljus. Krämen får verka i 3 timmar. Det verksamma ämnet i krämen ansamlas i de sjuka cellerna medan den friska huden inte påverkas.

- När krämen har fått verka torkas den bort. Om svår smärta förväntas kan patienterna få bedövning innan behandlingen startas. Bedövning ges som nervblockad (samma princip som vid bedövning hos tandläkaren). Därefter startas belysningsfasen som innebär att en lampa med rött ljus lyser på området i ca 9 minuter. I de sjuka cellerna sker en reaktion som gör att dessa förstörs. Smärtan som uppkommer vid PDT har beskrivits som stickande och brännande. Smärtan kan vara mer eller mindre uttalad beroende på

utbredning av skadad hud och var på kroppen förändringarna sitter. Oftast räcker det med vattenspray och samtal för att behandlingen skall kunna genomföras. Efter behandlingen är huden röd som vid en för lång vistelse i solen. På det behandlade området brukar sårskorpor uppkomma och huden fjällar men efter 1-2 veckor har det bildats ny frisk hud. Efteråt kan ibland en lätt rodnad ses men den försvinner successivt.

De främsta fördelarna med PDT är att det är en behandling som kan användas för att behandla stora utbredda områden. PDT är även lämpligt att använda på områden med sämre läkningsförmåga som t.ex. underben. Behandlingen medför också ett mycket gott kosmetiskt resultat vilket gör den särskilt lämplig på synliga områden som i ansiktet. Behandlingen görs under en halv dag på sjukhuset jämfört med andra behandlingar med krämer som behöver göras under flera veckor. Det kan vara besvärligt att själv smörja in vissa delar av kroppen t.ex. ryggen under lång tid.

Den främsta nackdelen med PDT är den smärta som kan uppkomma i samband med behandlingen. Det har i tidigare forskningsstudier visat sig att smärtan vid PDT kan vara svår att lindra.

I den första studien (Paper I) undersöktes alla patienter under ett år som behandlades med PDT på vår klinik för att identifiera faktorer som påverkade smärtan. Faktorer som kunde påverka smärtupplevelsen var storleken på behandlad yta, diagnosen som behandlades och lokalisation av förändringen. Det som gjorde mest ont var behandling av solskador i ansiktet och på hjässan.

I den andra studien (Paper II) undersöktes om transkutan elektrisk nervstimulering (TENS) kunde fungera som smärtlindring vid PDT av solskador i ansikte eller på hjässa. TENS är en behandling där en svag elektrisk stimulering ges via elektroder som fästs vid det smärtande området för att blockera smärtan. De flesta patienter uppnådde en viss smärtlindring med TENS men hos vissa patienter gav TENS ingen effekt. En enkät visade att patienterna tyckte att TENS var enkelt att reglera och de flesta skulle vilja använda TENS igen om PDT skulle göras i framtiden

I den tredje studien (Paper III) gavs nervblockad som smärtlindring vid PDT av solskador i panna och/eller på hjässan. Panna och hjässa bedövades på ena sidan och den andra icke bedövade sidan fungerade som kontroll. Nervblockad fungerade utmärkt som smärtlindring. Ett visst obehag upplevdes av patienterna vid injektionen ”sticket” när nervblockaden gavs men obehaget gick snabbt över. Vissa patienter upplevde inte heltäckande bedövning av hela behandlingsområdet.

I den fjärde studien (Paper IV) användes intervjuer för att undersöka och beskriva patienternas olika upplevelser av att behandlas på panna och/eller hjässa med PDT.
I intervjuerna kunde patienter 12 män och 4 kvinnor delge sina upplevelser och erfarenheter med egna ord beskriva hur det erfars och upplevs att behandlas med PDT både med och utan nervblockad. Resultatet av analysen visade sig i ett antal representativa teman med tillhörande kategorier av uppfattningar. Analysen av intervjuerna visade att PDT upplevs som mycket smärtsam som exempelvis att bränna sig på ett strykjärn men enligt patienternas utsagor var det värt smärtan när de såg resultatet. Majoriteten av patienterna upplevde att nervblockad gav smärtlindring men att injektioner som gavs vid nervblockad var obehagliga men att

det var snabbt övergående. Ett fåtal patienter upplevde oro innan huden blev normaliserad efter behandlingen.

Sammanfattningsvis är PDT en behandling av icke melanom hudcancer och dess förstadier som ger ett gott resultat. Denna avhandling visar att PDT kan vara och upplevas som mycket smärtsamt enligt patienternas erfarenheter, på gränsen till outhärdligt utan nervblockad särskilt i ansiktet och på hjässan. En fortsatt strävan efter att finna fler alternativ till smärtlindring är nödvändig, särskilt som det inte är möjligt att ge nervblockad på alla delar av kroppen samt att en del patienter upplever injektioner som obehagliga.

10. ACKNOWLEDGEMENTS

I would like to thank all of you who have inspired and supported me to perform this thesis. In particular, I would like to thank:

Ann-Marie Wennberg, my supervisor, for sharing your great knowledge, enthusiasm, and sense of humour. Many thanks for believing in me and giving me the possibility to perform research projects in "my own" research field. You have really inspired me to enter the world of research.

Helena Gonzalez, my assistant supervisor, for your engagement, great support and knowledge. You have always encouraged me when working on this thesis, especially when it felt heavy and troublesome.

Margret Lepp, my assistant supervisor, for your knowledge and inspiring guidance regarding qualitative studies. Without your support, I would not have been able to understand this "new world".

Olle Larkö, for your knowledge and support and for enabling me to perform research projects in my research field.

John Paoli, my co-author, for your knowledge and for your enthusiasm when performing studies; also for your outstanding patience while teaching me how to write in proper English.

Carin Sandberg, my co-author, for your encourage and support during this “journey”. You are a true friend.

Martin Gillstedt, my co-author, for your excellent, quick help with the statistical analyses. Thank you for your patient attempts to guide me in the field of statistics and help with many other things besides.

Marica B Ericson, my co-author, for your enthusiasm and never-ending patience in teaching me how to write academic articles.

The members of our research group, for enjoyable meetings and interesting discussions during our Monday afternoon meetings.

The staff at “Behandlingen”, Sahlgrenska University Hospital, for your commitment over the years, both when performing the studies and during the writing process.

Bo Stenquist, for your enthusiasm and much good advice and for sending me interesting articles to keep me updated in my research field.

Peter Dahm, for your excellent help teaching the dermatologist how to perform occipital NBs.

Clas Mannheimer, for kind help with feedback on the TENS-related parts of the thesis.

Inger Forsell, for your kind assistance with the administrative tasks of the thesis work and for help with many other things.

Morgan Carlsson, for your helpful assistance with photography.

My parents **Birgitta and Bo**, for always being there for me whenever I needed you and for always believing in me.

My brother **Johan**, for your enthusiasm and encouragement. You have always supported and believed in me.

My family **Hans, David and William**, for your support and love during this journey even when I did not always deserve it. Without your support, this thesis would not have been completed.

All **my patients** for participating in my studies.

This work was supported financially by the Edvard Welander Foundation and the federal government under the ALF agreement.

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12. PAPERS I-IV