

CLINICAL REPORT

Cold Water and Pauses in Illumination Reduces Pain During Photodynamic Therapy: A Randomized Clinical Study

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Pain is the main acute adverse event during photodynamic therapy of skin lesions. The objective of this randomized study was to evaluate the pain-relieving effect of pauses and cooling during illumination. Twenty-four patients with actinic keratoses were treated with photodynamic therapy in two symmetrical areas and cooled with either cold-water-spray or cold-water-pack (CoolPack). Treatment areas were cooled during either the first or second period of illumination, which were separated by a 3-min pause in illumination. Pain intensity was scored from 0 to 10. Water-spray reduced the mean pain score by 1.2 points ($p=0.030$) and CoolPack by 1.3 points ($p=0.007$) during the first half of the illumination. Pain intensity decreased during the pause by 3.7 points in water-spray patients ($p<0.0001$) and 3.0 points in CoolPack patients ($p<0.0001$). In conclusion, cooling resulted in a minor reduction in pain intensity, while adding the intermediate pause in illumination reduced the pain considerably. Use of pauses and cooling during illumination is an easy and inexpensive way to make photodynamic therapy more tolerable for the patient. **Key words:** photodynamic therapy; pain; cold water; pauses; PpIX fluorescence.

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The main acute adverse event during photodynamic therapy (PDT) is pain (1). Pain is described as a burning, stinging or prickling sensation in the treatment area only felt during illumination. The mechanism behind PDT-induced pain is unknown, but it is likely to be a consequence of nerve stimulation or damage by reactive oxygen species generated during illumination (2). The subsequent inflammatory reaction may also contribute to a prolonged weaker pain sensation.

Many initiatives have been taken to reduce PDT-related pain, for example, topical or injected local anaesthetics, cooling by fans or spraying water on the lesional area. Very few studies have evaluated the pain-relieving effects of these treatments. No effect could be related to topical anaesthetics (3–5), and a significant

reduction in pain score was observed when using cold air only during second PDT treatment (6).

Cryoanaesthesia with cold airflow, spray of cold water and ice packs is widely used in laser surgery and in PDT. The mechanisms of action may be two-fold. Lowering of the skin temperature will slow the conductivity of the peripheral nerves and therefore raise the stimulus threshold for pain sensation (7). The second mechanism suggested is a "counter-irritant" effect, which occurs when a temperature stimulus overrides a painful stimulus in the same area, thereby causing a reduction in the perception of the painful stimuli (8).

Cooling with a cold-water spray will result in drenching of the patient and flooding of the surroundings. To avoid this practical problem we introduced cooling using a cold-water pack (CoolPack) in this study.

The objectives of this study were to evaluate the pain-relieving effect of cooling by cold-water spray or cold-water pack (CoolPack) during illumination and to evaluate the effect of pauses in illumination when performing PDT on actinic keratoses (AK). We also evaluated whether photobleaching of protoporphyrin IX (PpIX) fluorescence was affected by the cooling procedures.

METHODS

Patients

Patients with symmetrically distributed AK were recruited from patients referred to the Department of Dermatology, Bispebjerg Hospital for PDT. The patients were in generally good health. Pregnant or lactating women were excluded. The protocol was approved by the ethics committee of Region Hovedstaden (H-KF-272867). Written informed consent was obtained from all patients.

Treatment

The patients were treated in two symmetrical treatment areas of equal sizes. The treatment area was measured, AK lesions were counted, and scales and hyperkeratoses were gently removed using a curette. Methyl aminolevulinate (MAL) cream (Metvix®, Photocure ASA, Oslo, Norway) was applied and the areas were covered with light-impermeable dressing for 3 h. After this time the remaining MAL cream was removed and the first treatment area was illuminated with red light-emitting diodes (LED) (Aktelite CL 128, Photocure ASA) using a total light dose of 37 J/cm² and a total illumination time of 9 min.

Patients were randomized to cooling by either cold-water spray or CoolPack and to cooling during the first or last halves of the

illumination period separated by a 3 min long illumination and cooling pause in all cases. Randomization was performed by drawing lots between opaque, sealed envelopes containing marked cards with "Water spray – in the first part of illumination", "Water spray – in the last part of illumination", "CoolPack – in the first part of illumination" or "CoolPack – in the last part of illumination".

The first treatment area was given as stated on the randomization card, and the second area was treated subsequently with the same cooling method but with cooling in the opposite half of the illumination.

Cooling

Cold water spray cooling was performed by spraying the treatment area with water at a temperature of 5°C every 10 sec immediately from the start of illumination and throughout the 4.5-min illumination period. Approximately 150 ml water was used for each illumination period.

CoolPack cooling was performed by covering the treatment area with a transparent plastic bag filled with 350 ml of water at 5°C. CoolPack was placed on the treatment area 30 sec prior to illumination and continued to cover the whole treatment area throughout the 4.5-min illumination period.

Skin temperature was monitored in the intervention group using a non-contact infrared thermometer (Raynger® MX4, Raytek Corporation, California, USA). Measurements were performed before illumination, at the beginning and at the end of the illumination break, and at the end of illumination. When cooling was performed using CoolPack skin temperature was also measured after the initial 30 sec of cooling prior to illumination.

Pain score

Patients scored their pain intensities before and after illumination and every minute during illumination with and without cooling. During the pause pain was scored immediately after the light was turned off and just before illumination continued. Pain was assessed using a numerical scale ranging from 0 to 10, on which 0 = no pain and 10 = worst imaginable pain. Mean pain score was calculated as the mean of the 4 pain scores given by the patient during each half of illumination.

PpIX fluorescence

MAL-induced PpIX fluorescence in the treatment areas was measured using a fluorescence camera (Medeikonos PDD/PDT, Medeikonos AB, Gothenburg, Sweden). The excitation wavelengths were 365nm and 405nm and the illumination time was 2 sec. The amount of PpIX fluorescence was calculated from the photographs using a MatLab® program (MatLab® 7.2.0.232, MathWorks, Natick, USA). Each picture was calibrated using a fluorescence standard (Uranyl Standard; J&M; Analytische Mess und Regeltechnik GmbH, Germany). MAL-induced PpIX fluorescence was measured in arbitrary units (AU) and defined as pixels having a value of 2500 above the background picture (9).

PpIX photos were taken before and after illumination, as well as during the break between the two illumination periods.

Data analysis

Aiming for a significance level of 0.05 and a power of 0.80, and on the assumption that the smallest clinically important mean difference in pain score was 2.1, and the standard deviation (SD) of the difference in pain score was 2.6, we calculated that at least 12 patients should be included in each cooling group (Altman normogram for sample size calculation). All statistical analyses were performed using GraphPad Prism version 4.03 (GraphPad

Software Inc, San Diego, USA). Since data was normally distributed (Kolmogorov-Smirnov Test) we used parametric statistics. Means and SD are used throughout. We used a paired *t*-test to compare paired data and an un-paired *t*-test for un-paired data. *p*-values less than 0.05 were considered significant.

RESULTS

Patients

Twenty-four patients with AK participated in the study (17 men, 7 women, mean age 67 (SD ± 13) years). Ten patients were treated in symmetrical areas on the face and scalp, 3 patients on the trunk, 4 patients on the legs, and 7 patients on the back of the hands. The mean size of the treatment areas was 112 (SD ± 43) cm² and the mean number of AK lesions in each treatment area was 24 (SD ± 16), with no difference between the two treatment areas (*p* = 0.77 and *p* = 0.63). No differences in age, gender, size of treatment areas and number of AK lesions were found between the water spray patients and CoolPack patients (*p* = 0.61, *p* = 0.65, *p* = 0.64 and *p* = 0.70).

Pain score

Cooling significantly reduced the mean pain score during illumination, as seen in Table I.

Cooling during the first half of the illumination using water spray reduced the mean pain score by 1.2 points and using CoolPack by 1.3 points (Fig. 1). No differences in pain score were found between the two cooling methods (*p* = 0.90).

During the intermediate 3-min pause, the pain intensity decreased rapidly, with a mean reduction of 3.7 pain score points in the water spray areas and 3.0 pain score points in the CoolPack areas (*p* = 0.28).

Table I. Mean pain scores (standard deviation) during first and second halves of illumination with light-emitted diodes (LED) and just before the start and end of the illumination break. Cooling with water spray or CoolPack was performed only during either the first or the second half of the illumination. Pre-treatment with Metvix® was a standard procedure (*n* = 12)

	LED illumination		
	First half	Pause	Second half
No water spray cooling	4.9 (2.3)		3.5 (2.0)
Water spray cooling	3.6 (2.2)		2.2 (1.9)
	<i>(p</i> = 0.030)		
Just before pause start		5.0 (2.4)	
Just before pause end		1.3 (1.2)	
		<i>(p</i> < 0.0001)	
No CoolPack cooling	4.9 (2.6)		3.3 (2.3)
CoolPack cooling	3.6 (2.7)		2.1 (1.8)
	<i>(p</i> = 0.007)		
Just before pause start		5.3 (3.0)	
Just before pause end		2.3 (2.0)	
		<i>(p</i> < 0.0001)	

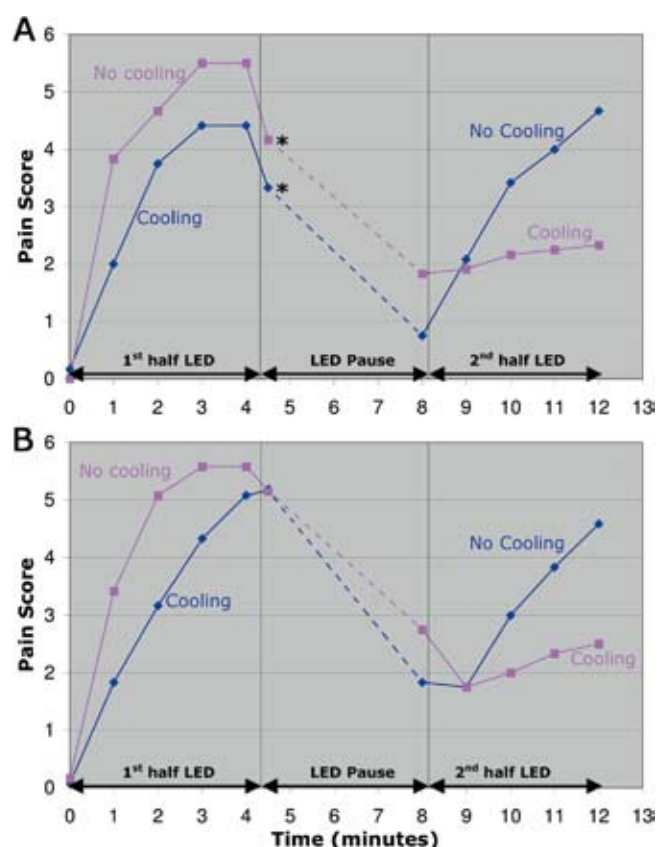


Fig. 1. Mean pain scores (0–10) during illumination with light-emitting diodes (LED) for treatment areas cooled with (A) cold-water spray or (B) cold-water-pack (CoolPack). One area was cooled during the first half of the illumination and not during the second half, and the other area was cooled at the opposite times. A 3-min pause was carried out between the two halves of illumination. *Immediate fall in pain intensity when illumination is stopped.

Cooling during the last half of the illumination using water spray reduced the mean pain score by 1.4 points and using CoolPack by 1.1 points. No differences in pain score were found between the two cooling methods ($p=0.75$).

Cooling during the last half of the illumination period significantly reduced the pain intensity compared with the non-cooled first half ($p<0.0001$) (Fig. 1).

If cooling was performed during the first half of the illumination period the mean pain was reduced to the same level as during the second half of the illumination without cooling ($p=0.45$).

Pain scores without cooling were higher during the first half of the illumination period (mean 4.9) than during the last half of the period (mean 3.4, $p<0.0001$), probably because the amounts of PpIX to be activated is larger during the first half of illumination and pain intensity decreases during the illumination pause.

Skin temperature

Skin temperatures increased in un-cooled treatment areas by 2.1°C ($\pm 1.3^{\circ}\text{C}$) during the first 4.5 min and 2.9°C ($\pm 2.1^{\circ}\text{C}$) during the last 4.5 min of illumination.

Water spray cooling decreased the skin temperatures by 6.4°C ($\pm 4.0^{\circ}\text{C}$) and 8.7°C ($\pm 3.9^{\circ}\text{C}$) during the first and last halves of the illumination period, respectively.

CoolPack was placed over the treatment area 30 sec prior to illumination, resulting in a mean decrease in skin temperature of 12.6°C ($\pm 5.4^{\circ}\text{C}$). When CoolPack was placed on the skin the temperature of the water pack was 5°C and after the 4.5 min illumination the temperature of the water pack had increased by approximately 10°C .

Using CoolPack during the first 4.5 min of illumination resulted in a mean decrease in skin temperatures of 9.4°C ($\pm 3.8^{\circ}\text{C}$) and using CoolPack during the last half of the illumination resulted in a mean decrease of 9.9°C ($\pm 2.2^{\circ}\text{C}$).

CoolPack resulted in a larger decrease in skin temperature during the first part of illumination compared with water spray cooling ($p=0.029$), whereas no significant differences were seen during the last part of illumination ($p=0.37$).

PpIX fluorescence

Photobleaching of PpIX during illumination can be seen in Table II.

The first 4.5 min of illumination resulted in a mean photobleaching of the PpIX fluorescence of 83% in the area cooled with water spray and 90% if no cooling was performed ($p=0.11$). After completing the illumination 96% of the PpIX fluorescence was bleached if cooling was performed in first half of the illumination only and 93% if cooling was performed in the last half of the illumination only ($p=0.29$).

Cooling with CoolPack in the first half of the illumination resulted in less photobleaching (mean 75%) of PpIX fluorescence than no cooling (mean 90%, $p=0.001$). Ninety-five percent photobleaching was obtained at the end of illumination regardless of when CoolPack cooling was applied during the illumination period ($p=0.88$).

Table II. Mean percent photobleaching (SD) of protoporphyrin IX (PpIX) after first and second halves of illumination with and without cooling with water spray or CoolPack. Cooling was performed only during either the first or second half of the illumination ($n=12$)

	LED illumination	
	After first half	After second half
No water spray cooling	89.9% (16.1)	95.6% (7.6)
Water spray cooling	82.9% (14.8)	92.6% (14.7)
	$(p=0.11)$	
No CoolPack cooling	90.3% (8.9)	95.1% (8.1)
CoolPack cooling	75.3% (16.0)	95.4% (5.0)
	$(p=0.01)$	
	$(p=0.88)$	

LED: light emitted diode; ns: not significant.

DISCUSSION

This randomized within-patient study shows that cooling during illumination reduces pain associated with PDT.

However, both cooling methods gave only small reductions in pain scores, of approximately one point. Most patients reported that cooling made the treatment much more tolerable, which nevertheless does not correlate very well with the minor pain reduction. Psychological aspects, such as the calming effect of someone trying to reduce the pain or the constant presence of a nurse during the cooling procedures, may influence the patient's perception and thus constitute confounding factors of our results.

We found no differences in the mean pain-relieving effect between the two cooling methods. However, Fig. 1 shows a difference in how the two methods are cooling. Water spray provides constant pain reduction throughout the illumination period, while CoolPack provides a high pain reduction at the beginning of the illumination but less at the end. An explanation for these differences might be that part of the cooling process is caused by water evaporation, which does not occur with the CoolPack. In addition, the cold-water spray maintains the same temperature throughout the illumination, while the CoolPack increases in temperature by the end of the 4.5-min illumination. To obtain the maximal effect of CoolPack cooling it would probably be necessary to exchange the packet at least twice during illumination. However, with the cold water spray technique it is important to initiate spraying at the beginning of the illumination period and to make frequent repeat sprayings, as a late onset of spraying with infrequent repetitions might compromise the cooling effect. In the course of daily clinical work these drawbacks may support the use of CoolPack cooling, which does not require the presence of a nurse during the entire illumination period.

One study has evaluated the analgesic effect of cold air during PDT of basal cell carcinomas and Bowen's disease (6). One lesion was treated with cold air and one without during two PDT treatments of two symmetrical lesions. In accordance with our results, this study showed a minor effect of cooling and the pain-reducing effect was only significant during the second treatment. The study did not use a numerical pain scale, but instead Wong-Baker Faces Pain Rating scale, which makes direct comparison between the two studies a little difficult. Cold air is often used to cool the treatment area, but the use of water spray and CoolPack is simpler and much cheaper as no special equipment is needed.

If no cooling or pauses are performed during PDT the pain intensity will increase within the first 3 min of illumination to a level that will be constant for the rest of the illumination period (Fig. 2). These data were ob-

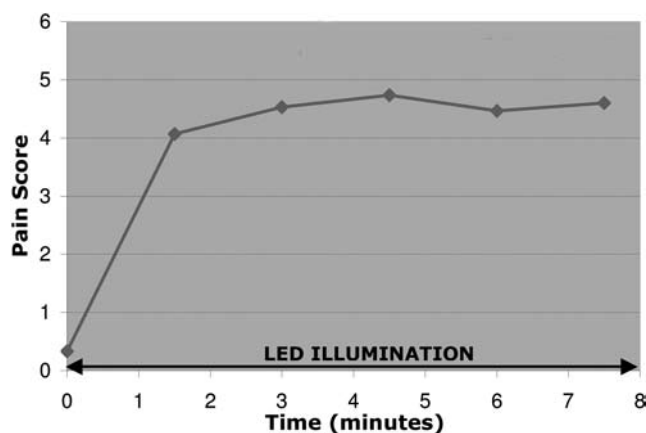


Fig. 2. Mean pain scores (0–10) during methyl aminolevulinate-photodynamic therapy (MAL-PDT) of 15 other patients treated for actinic keratoses in the face and scalp. MAL cream was applied for 3 h following the gentle removal of scales and hyperkeratoses. The treatment area was illuminated with red light-emitting diode (LED) light using 37 J/cm². No cooling or pause was performed during illumination.

tained by treating 15 other patients with AK on the face and scalp using exactly the same treatment procedure without cooling or breaks.

The increase in pain score to a certain constant level is seen in this study also (Fig. 1), but we performed a 3-min pause halfway through the 9-min illumination. When the lamp was turned off the pain score decreased immediately, as seen in Fig. 1A. During the pause the pain score was reduced significantly by an average of 3.4 pain score points. If no cooling was performed after the pause the pain score gradually returned to the same level as before the pause. With cooling of the treatment area after the pause it was possible to keep the pain score in the lower level achieved during the pause.

Our study shows that a pause in illumination is a highly effective way to reduce the pain and even more effective than cooling during the illumination. A good way to reduce pain during PDT may be to have a pause 3 and 6 min into the illumination, possibly in combination with cooling.

Patients did find cooling with cold-water spray comfortable despite the drenching. A few patients found the CoolPack a little uncomfortable when it was initially placed directly on the skin, whereas the sensation changed to comfortable during the last half of the illumination where the intense effective cooling of the warm and burning skin was highly pain-relieving.

Cooling with CoolPack resulted in a significant reduction in photobleaching of PpIX fluorescence. This finding was not surprising since the illumination was performed through the CoolPack, which absorbed approximately 20% of the light dose.

We do not expect a reduced treatment efficacy due to the reduction in light dose because 75% of the PpIX had already bleached during the first half of the illumination and because previous studies have shown that the light

dose used for PDT is more than sufficient to activate the accumulated PpIX (10). However, the design of this study did not include follow-up visits and therefore, no firm conclusions can be made on cure rates.

The decrease in skin temperature results in vasoconstriction of the capillaries in the upper dermis and might also slow down the enzymatic processes and thereby reduce the phototoxic reaction, which is considered to be important for the PDT response.

It is generally believed that the photodynamic effect is associated with the rate of photobleaching, which was not affected by water spray cooling. Since our study design did not include follow-up visits we could not evaluate the PDT-induced inflammation or cure rate of the treatment.

In conclusion, cooling during illumination resulted in a minor reduction in pain intensity during PDT. Moreover, an intermediate pause reduced the pain considerably. Water spray cooling did not affect the photobleaching of PpIX. The use of pauses and cooling during illumination is an easy and inexpensive way to make PDT treatment more tolerable for the patient.

Conflicts of interest: Merete Hædersdal received a fee from Photocure ASA, Norway for organizing educational sessions. Hans Christian Wulf received a fee from Photocure ASA, Norway for organizing educational sessions and speaking. Stine Regin Wiegell received a fee from Photocure ASA, Norway for speaking at the above-mentioned educational sessions.

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