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Post procedural pain with photodynamic therapy is more severe than skin surgery

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Actinic keratoses;
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Summary *Objective:* To compare prospective data on pain experienced by patients undergoing large facial skin cancer surgery with pain experienced with novel face photodynamic therapy (PDT).
Design: A comparison of pain data sets from two prospective trials in the same centre.
Setting: Referral skin cancer centre in Australia.
Protocol: 34 PDT patients had two aminolevulinate treatments to the face two weeks apart. 68 Surgery patients, matched 2:1 for gender and age, had large skin cancer excisional surgery to the face and closure with flap, graft or wedge reconstruction.
Main outcome measure(s): Severity of pain during and following procedure.
Results: The only patients describing their experience as the worst pain of their life were 4 PDT patients (12%). The median and mean pain scores for PDT patients were significantly higher than for extensive facial large face surgery, ($p < 0.001$). Further analyses comparing PDT to patients having all skin cancer surgery on the face ($N = 170$) matched for gender and age demonstrated more pain experienced with PDT. PDT is significantly more likely to result in pain requiring strong analgesia or pain beyond strong analgesics than skin cancer surgery including large facial operations.
Discussion and conclusions: Clinicians should consider explaining the relative likelihood of more severe pain whenever PDT is considered over surgery. The pain experienced with this PDT product may not reflect the pain experienced with other PDT products.

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Introduction

Photodynamic therapy (PDT) has become an established option in the management of skin cancers[1–3] and precancerous skin lesions.[4–7] It has emerged as an option that can be offered as an alternative or adjunct to surgical excision.[2,8]

PDT active ingredients are applied to the affected skin and a light source is then applied to the skin for an illumination following an incubation period. The active ingredient is absorbed and intracellularly converted to protoporphyrin IX, a light-reactive intermediary protein. Activation of protoporphyrin IX by the PDT light source creates free radicals which are essential to the mechanism of action.

Patients commonly perceive surgery, including skin surgery, as a painful experience.[9–11] PDT has also been reported to frequently cause pain.[12–15] When patients have two treatments of PDT pain is frequently severe with the second treatment.[15] Pain can be more severe when a larger field is treated with PDT.[12] Kasche[16] demonstrated that pain during activation can be such that patients request discontinuation of treatment before reaching the required light dose has been reached. This was more likely if the patient was being treated with aminolevulonic acid (ALA) than if treated with methyl aminolevulinate (MAL). There is a report that pain experienced with PDT in Australia may be greater than elsewhere.[17] Patient pain perceptions may lead them to seek a topical alternative to an invasive approach in the hope that their procedure and post-procedure pain experience will be reduced.[18]

In 2007[19] we published a prospective study of patients' perceptions of their skin cancer surgery. Included in those perceptions we detailed the level of pain experienced by patients following such surgery.

We have since completed another prospective study involving photodynamic therapy with a novel preparation of ALA (Novel ALA) being used as the active ingredient. As part of the protocol for this PDT trial we prospectively recorded the pain patients' experienced during and following their PDT treatment. We now report on the post procedural pain experiences and compare them to the patients that underwent surgery.

The novel ALA product used to treat the patients described herein was developed by Allmedic Pty Ltd as a simple, premixed preparation and was promoted as having a prolonged shelf life and requiring a low intensity of activating light. The aim of the study was to compare a prospective database of patients undergoing skin surgery with a prospective database of patient undergoing PDT. The post procedural pain levels experienced by patients having skin cancer surgery including major skin cancer surgery to the face is to be compared with PDT patients.

Methods

The PDT protocol was approved by Bond University Human Research Ethics Committee. The post procedural pain data following skin cancer surgery was acquired as part of completion of a randomized controlled trial approved by the Barwon Health Research and Ethics Committee.

The primary PDT trial sponsor was Allmedic Pty Ltd (Taren Point, NSW, Australia). There was no sponsor for the surgery protocol.

All patients were managed in a single skin cancer referral centre in southern Australia.

Prospective data on the pain expectations of skin cancer surgery in this centre have been previously reported.[19] From this data set of 576 patients, we age and gender matched patients that had more substantial skin cancer surgery to the face 2:1 for each PDT patient. The extensive facial skin cancer surgery group was defined by resections requiring closure by large full thickness wedge repair, full thickness skin grafting or larger random pattern or interpolation skin flap reconstructions or axial flap repairs. This extensive facial surgery group was the key control group of 68 patients.

We also compared 170 patients (all facial surgery group) that had undergone all types of skin cancer surgery to the face (age and gender matched 5:1) to PDT patients. We further compared the whole surgery data set of 576 patients (all skin surgery group) to PDT patients.

Patients treated with novel ALA for actinic damage had previously experienced one or more histologically proven and surgically cleared facial skin cancers. The protocol involved two PDT treatments 14 days apart. The patient was provided with a 10% alpha hydroxy acid solution to reduce thickened hyperkeratoses to be used twice daily for two weeks prior to PDT. Following a test dose, novel ALA (20% 5-aminolevulinate solution) was applied to the whole face [except for eyelids and near mucosal surfaces] followed by a five hour incubation period during which exposure of light face to the face light was avoided. The border of the face was defined as the hairline superiorly, anterior to the tragus laterally and the lower margin of the mandible inferiorly.

A 30 min illumination was then undertaken with the PDT light source provided by the sponsor (465 nm blue LED light at 48 J/cm^2 for 20 min and then 625 nm red LED light at 64 J/cm^2 for 10 min). The sponsor advised that efficacy and safety of their trial ALA had been optimized with this light source. They advised that a combination of blue and red lights was designed to allow for two levels of penetration within the skin. Incubation involved the liquid being massaged into each side of face to provide a thin and uniform cover. Prior to illumination, the face was washed with warm water and dried. During illumination, the eyes and eyelids of the patient were shielded from the light source. Each patient had an attendant(s) present at all times during illumination. A fan to reduce burning sensations was provided as required. The treatment was paused if requested by the patient and discontinued if unable to be tolerated.

Following treatment, the patient was given extensive advice regarding minimizing sun exposure, analgesia etc. They were encouraged to remain indoors in a darkened room for at least 48 h and were provided with a sunscreen to apply when outside both before and after treatment.

At follow up, patients in both studies were asked by the nursing staff to rate their level of pain experienced post procedure. The level of pain was classified as follows; 1) no pain experienced, 2) mild pain that did not require analgesia, 3) pain that was relieved with paracetamol (Panadol®, Herron Paracetamol® or Panamax®), 4) pain that required stronger oral analgesics to obtain relief such as