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A Randomised Assessor Blinded Comparison of Low Irradiance and Conventional Irradiance Photodynamic Therapy for Superficial Basal Cell Carcinoma and Bowen's Disease

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Conflicts of interest: S Ibbotson has received conference expenses and honoraria from Galderma; JF and IDWS are founders and shareholders of Ambicare Health Ltd, which has developed wearable light sources for skin cancer and acne treatment. Ambicare Health Ltd. provided the Ambulight devices free of charge for use in this study but did not have any academic, intellectual or financial input into the study.

Dear Editor, The inconvenience and pain of hospital-based photodynamic therapy (PDT) is sometimes limiting.[1] We developed very low irradiance LEDs for ambulatory PDT. Preliminary studies showed this to be convenient and relatively painless.[1-4] Here we evaluate the Ambulight® device (Ambicare Health Ltd) in a randomised controlled assessor-blinded study comparing low irradiance ambulatory PDT (APDT) with conventional PDT (CPDT) for superficial basal cell carcinoma (SBCC) and Bowen's disease (BD) (lesions ≤2cm). The trial was East of Scotland Research Ethics Service REC 2 approved and registered (clinicaltrials.gov NCT02872909).

The study is outlined (Figure 1a). Patients (one lesion each) were randomised to APDT or CPDT (2:1; APDT:CPDT). All lesions were gently scraped (disposable ring curette (Stiefel®)). Methyl aminolevulinate (MAL; Metvix cream 16% w/v, Galderma UK) was applied and occluded for three hours prior to irradiation (Aktilite® 128; peak wavelength 636nm; full width half maximum (FWHM) 18nm; 85mW/cm^2; 75J/cm^2; approximately 17 minutes) in CPDT.

For APDT, immediately after MAL application the Ambulight® device was secured to the site by its adherent coating and connected to a battery pack (in/on pocket/belt). This was automated "off" for three hours before irradiating for three hours (peak wavelength 640nm; FWHM 25nm; 7mW/cm^2; 75J/cm^2).

Treatment was repeated at one week for each study arm (First cycle). Clinical outcome was assessed at week 12 and a repeat cycle undertaken if not clear. Pain (visual analogue scale (VAS; 0-10) for maximum pain during PDT) and phototoxicity (erythema: 0-3; none, mild, moderate, severe) were assessed at one week. VAS scores for first and second treatment were averaged as treatment cycle pain scores. Clinical outcome (clear (CR)/partial response (PR)/no response (NR)) was assessed at six and 12 months. Patient evaluation of treatment (overall satisfaction VAS 0-10; including perception of efficacy, adverse effects and convenience) was undertaken at last visit.

Pain was the primary study endpoint, with efficacy, erythema and patient satisfaction as secondary endpoints. Pilot data using prototype APDT, showed a mean pain score of 1.25 (SD 0.4; n=12) compared to 5.26 (SD 2.38; n=50) for CPDT.[4] For 90% power to detect as significant at 5% level ($p<0.05$), a difference in mean pain score in one group of 2 compared with 4 in the other

group, assuming two-sided testing and unequal randomisation, a minimum of 36 subjects was needed (50 accounting for drop-outs). Random sequence was computer-generated and allocations concealed in opaque envelopes. Study investigators were blinded until database lock and the data analyst (RD) was unblinded after initial analysis. VAS for pain and patient satisfaction were not normally distributed but with log transformation, parametric methods could be used for comparisons using unpaired t-tests, with back-transformation to present as fold-differences. Erythema scores were compared using Mann-Whitney *U* test. Comparisons of proportions were by chi-square tests.

Fifty-two were randomised (two withdrawn as device failures) (Figure 1b). Median age was 71 (range 41 to 87) years; 35 women. Thirty-two received APDT and 18 CPDT. Twenty-seven had SBCC (19 APDT) and 23 had BD (13 APDT). Twenty-six lesions were on legs, 17 on trunk, six on arm and one on head/neck. There was no significant difference in lesion site distribution between APDT/CPDT (p=0.21). Median lesion size was 1.2 (0.5 to 2) cm, with no significant difference between study treatments (p=0.75).

Geometric mean VAS pain scores were 1.55 for APDT and 2.62 for CPDT (p=0.36) (Figure 1b). Of the APDT group, 77.8% (-6.6%, 95% confidence interval for difference -30% to 16%) were clear at one year compared with 84.4% with CPDT (p=0.56).

Erythema was slightly greater with APDT (median 2) (CPDT median 1; 95% CI for difference 1 to 0, p= 0.025). Geometric mean patient satisfaction scores at one-year (available for 24 APDT, 14 CPDT) were 9.63 and 9.27 for APDT and CPDT respectively (p=0.34).

The effective use of this wearable device enhances potential for home-based PDT, which appeals for patient-centred care and is particularly relevant in the pandemic recovery period. Interestingly, pain during PDT for small lesions of SBCC and BD was low for both APDT and CPDT, with a non-significant trend to slightly lower pain scores with APDT, unlikely to be of clinical relevance. Clearance rates at one year and patient satisfaction levels were high for both APDT and CPDT.

CPDT-induced pain was less than anticipated compared with a cohort, including larger lesions.[5] Thus, PDT for small SBCC and BD lesions is well tolerated, with low pain scores and high

clearance rates, whether using higher or low irradiance LED devices.[3,5,6] These findings support the use of low irradiance portable LED-based PDT as a well-tolerated, effective and convenient option for selected patients.

References

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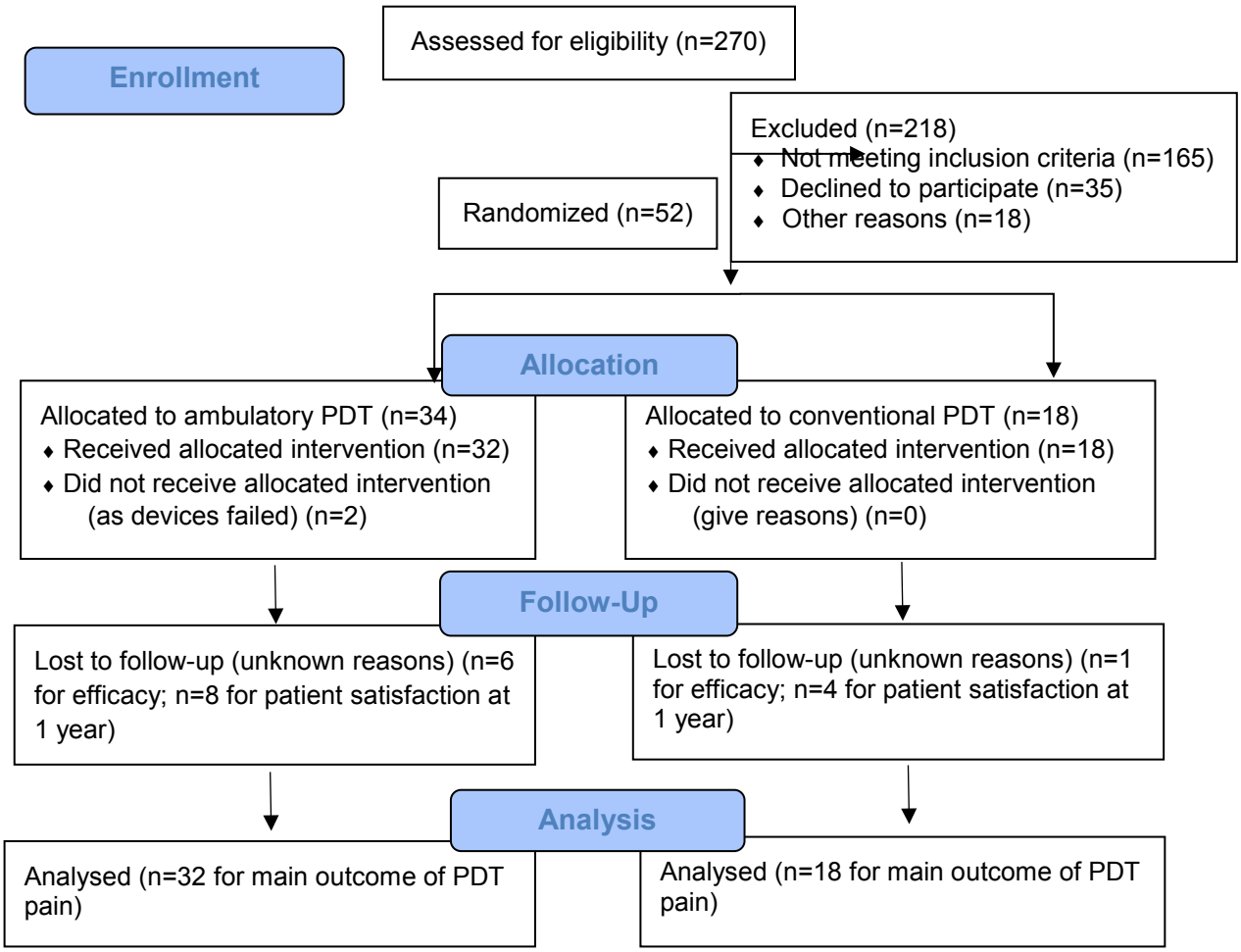
Figure Legends

Figure 1a: The study outline from assessment of participants for eligibility through to analysis

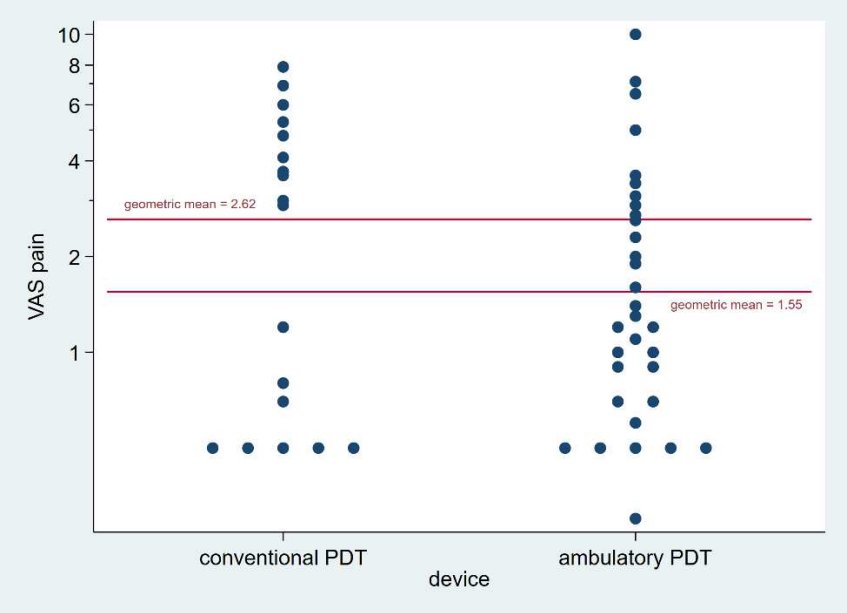
Figure 1b: PDT treatment cycle pain scores for CPDT (n=18) and APDT (n=32). The geometric means are indicated.

CONSORT 2010 Flow Diagram

(1a)



(1b)



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1. Layton A. Reviewing the use of Fludroxycortide tape (Haelan Tape) in Dermatology Practice. Typharm Dermatology.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Typharm Limited on 02037 694160.

1/FT/12/2106/554 and Date of Preparation: June 2021