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Early Laser for Burn Scars (ELABS) - Randomised controlled trial of pulsed dye laser treatment and standard care versus standard care alone for the treatment of hypertrophic burn scars

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ABSTRACT

Background: Hypertrophic burn scarring (HBS) is described as "the greatest unmet challenge after burn injury". This ELABS trial hypothesised that early pulsed dye laser (PDL) treatment of HBS improves both scar quality and quality of life (QoL).

Methods: A parallel arm randomised controlled trial to assess the effectiveness and cost-effectiveness of PDL was undertaken at seven centres in the UK. Patients were eligible if their burn injury was within three months of wound healing, and ineligible either with history of keloid scarring or aged < 16 years. A total of 153 (77 male, 76 female) participants were recruited between Nov 17, 2021, and Jun 30, 2023, and were randomised using software in a 1:1 ratio stratified by study centre; 138 (69 each arm) were included in the final complete-case analysis. Both study arms received standard care, and the intervention arm received three PDL treatments. The primary outcome was patient-rated scar quality (POSAS) at six months. The trial was registered with International Standard Randomised Controlled Trial Number registry (ISRCTN14392301).

Findings: Early PDL showed a statistically significant improvement in patient-rated scar quality ($p = 0{\cdot}041$) and the secondary outcome, participant's perception of change in scar quality ($p = 0{\cdot}01$), at six months. There were no statistically significant differences for Quality-of-Life, observer-rated POSAS scar quality, or colour measurement. Early PDL was not cost-effective at 6 months follow-up for the willingness-to-pay threshold of £20,000 per Quality-Adjusted-Life-Year (QALY). There were no unexpected adverse events related to the intervention.

Interpretation: Early PDL treatment of HBS is safe and shows improvement for patient-rated scar quality but not QoL at six months. As scar maturation is prolonged and dynamic, longer-term follow-up of upwards of two years is required both to understand the eventual clinical effect on scar outcome and to make any definitive conclusion concerning cost-effectiveness.

1. Introduction

Hypertrophic scarring is characterised by being red, raised and firm and, in contrast to keloids, remains within the borders of the original wound. It occurs following skin insults associated with excessive inflammation, but surgical, traumatic or burn-related wounds are more

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common causes. More than 100 million people worldwide are thought to have acquired scars due to these injuries.[1]

Survival rates from major burns have improved significantly, particularly for injuries of greater total body surface area (TBSA). Early excision and skin grafting is known to reduce infection and decrease the severity of scarring but does not prevent it.[2] Burn injuries that have not healed within 21 days have a greater likelihood of developing scars.[3] Almost invariably, burn survivors with wounds which heal slowly develop symptomatic, life-changing hypertrophic burn scarring (HBS).

HBS impacts patients both physically and psychologically. Physical symptoms include itch, pain, tightness and limitation of joint mobility. Psychological symptoms include issues with aesthetic appearance and body image, insomnia, heightened emotion and low self-esteem. Both often lead to workplace absenteeism and psychosocial issues.[4] The need to improve outcomes for burns survivors with HBS has been described as, "The greatest unmet challenge after burn injury."[5]

HBS is difficult to treat. Few randomised controlled trials exist to inform evidence-based scar management. This leads to a lack of consensus globally as to the optimal treatment regimen.[6] HBS treatment is further confounded by factors such as variable scar presentation, and non-standardised, multi-modal treatment.

Standard of care (SC) treatment includes moisturisation, silicone gel, pressure therapy, corticosteroid injection, and splinting. Pulsed dye laser (PDL) and ablative fractional laser (AFL) treatment are used based on anecdotal and case-control study evidence.[7] Randomised controlled trials of laser treatment for HBS have shown the efficaciousness of carbon dioxide AFL.[8,9] However, clearer evidence is required for the effect of early PDL and this study will focus on PDL alone.

There are fundamental differences between PDL and AFL for parameters such as wavelength and power, which determine both their mechanism of tissue interaction and their effect on scar symptoms. AFL works to ablate tissue by vaporisation in a highly localised spatial orientation. It can reduce volume, thickness and stiffness of HBS through the creation of microthermal zones in order to stimulate collagen remodeling and regeneration of skin tissue.[7] Conversely, PDL disrupts the neovascularisation which drives the formation of HBS.[10] This implies that PDL could be most effective by its implementation during the early stages of scar maturation. Subsequently, scar progression may be diminished by dampening of the inflammatory and proliferative phases, and indeed where redness persists. In this way, the scar maturation may be shortened, and the final scar outcome may be improved in respect of redness, itch, pliability, thickness and texture.[11–13] Early scar intervention is recommended, underpinned by the premise that it is easier to prevent an excessive and dysfunctional microcirculation than to treat it once formed.[14]

The Early Laser for Burn Scars (ELABS) trial hypothesised that early PDL treatment of HBS has increased benefit than when HBS is established.[15] The aim of ELABS was to assess early PDL treatment of HBS within three months of wound healing, as defined by complete epithelialisation. The protraction of time-point for "early" initiation of PDL to less than 3 months saw a compromise. The logistics of identification and enrolment of recruits needed sufficient time, and consideration was made that PDL treatment of newly healed skin may induce wound regression. The clinical effectiveness and cost-effectiveness of this approach, in conjunction with standard care, were investigated compared to standard care alone. Both scar quality and quality of life (QoL) were measured to evaluate the effect on scar outcome from the patient's perspective.

2. Methods

2.1. Study design

A national, multicentre parallel arm randomised controlled trial was conducted across seven National Health Service (NHS) hospitals in the United Kingdom. ELABS was approved by The South-West Research Ethics Committee (REC reference 21/SW/0049). The protocol was published:[16] https://doi.org/10.3310/nihropenres.13234.1

A Patient and Public Involvement (PPI) cross-sectional group of 18 people (6 male, 12 female; mean age (range): 44 (16 to 79)) years was consulted on study design. The session was overseen by an independent facilitator. The group agreed that ELABS was necessary, as all patients who received PDL for burn scars perceived benefit over SC. The group voted for early PDL as the study intervention (10 vs. 8) in conjunction with SC. The control was SC alone as sham laser treatment was deemed non-viable due to the associated inherent stimuli of laser treatment. The group felt that PDL could be delayed by 6 months for the control arm as it is known to be effective where redness persists.[17] There was no perceived detriment for delayed treatment as this time frame was commensurate with the current laser treatment pathway. The PPI group was consulted, remained informed and gave feedback throughout the study.

2.2. Participants

Patients with burn injuries of greater than 1 % total burn surface area (TBSA) were eligible if they were treated with skin grafts or had conservatively managed wounds or donor sites which: had delayed healing of more than two weeks; had potential for HBS; were suitable for scar management therapy; and were within three months of the wound healing, as defined at the time point of full epithelialisation when dressings were no longer required. Patients were not considered eligible for inclusion if they were: unable to give informed consent; below 16 years-of-age; or prone to, or had a family history of, keloid scarring.

Participants gave written consent having been provided with all relevant information through both patient information sheets and in-person consultations with the recruitment team. Demographic data were obtained at baseline from the patient and their clinical records. Age and gender were recorded. Skin typing was evaluated using the standard sixteen group classification of ethnicity currently used in the UK, in addition to completion of the Fitzpatrick skin type scale by the assessor and participant.[18] The following parameters known to affect the likelihood of scarring were also recorded: depth of burn; anatomical location, categorically defined as head/neck, torso or limbs; TBSA; aetiology of the burn injury; and time taken for the wound to heal.

Where multiple scars were present, the scar having the greatest impact, as reported by the patient, was defined as the 'study scar'. Only one scar per patient was included. Whichever study group the patient was assigned to, the same study scar was assessed and treated each time. The study scar and two regions of interest (ROI) were selected at baseline. The approximate size of the study scar was up to 500 cm^2, but typically, around 100–250cm^2. The minimum size for the study scar was a 4 cm square, which was the defined size of a region of interest ('scar ROI') within the study scar. The 'comparison ROI' was identified as a contralateral, unburnt area of skin of similar size. If the contralateral area was burnt or scarred, then an unburnt area proximal to the scar ROI was selected. Each ROI was used for the colour measurements only. Photographs were taken at baseline to identify the location of the study scar and the ROIs to precisely relocate these areas at subsequent assessments.

2.3. Randomisation and masking

Blinded assessments of observer-rated Patient and Observer Scar Assessment Scale (POSAS) and colour measurement were performed by a trained healthcare professional, such as burn surgeon, therapist, nurse or scientist, at baseline prior to their allocation. On completion of baseline data entry, participants were allocated to a trial arm using a randomisation tool within a secure web application (REDCap Cloud). Randomisation was in a 1:1 ratio, stratified by study centre and using random permuted blocks of varying size from 2 to 6.

Allocation status of the participant was communicated by e-mail to the principal investigator (PI) and their delegated treatment team. Allocation was revealed to the participant by the PI, or delegate, but was masked from the blinded assessor. Participants were instructed not to divulge their allocation to the blinded assessor at primary endpoint. No deviations to protocol were recorded for unblinding.

2.4. Procedures

2.4.1. Control arm

The control arm received SC alone at 0, 6 & 12 weeks, where week 0 was within two weeks of allocation. SC treatment was dependent upon scar maturation and clinical need. It included: moisturisation and massage; silicone gels, topical or sheeting; and compression garments.

2.4.2. Intervention arm

The intervention arm received a course of three PDL treatments at intervals of 6 weeks (0, 6 & 12 weeks), in addition to SC. The treatments were performed in either order for each study visit. The PDL (Cynergy, Cynosure, Westford, MA, USA or Vbeam, Syneron Candela, USA) treatment settings used for Fitzpatrick skin types I-III and low IV were: wavelength, 595 nm; spot size, 10 mm; pulse duration, 0·5 or 0·45 ms; energy fluence, 5 – 9 J cm^{-2}; 10 % overlap permitted; single pass.

Laser treatment was performed by a trained laser operator. The energy fluence was selected, and increased, to produce a moderate to strong purpura without the presence of skin blanching. Once the desired response was observed, the operator treated the entire study scar. Previous laser settings were used at subsequent treatments, but the operator could increase the fluence until the desired response was again achieved.

For darker skin types with high type IV or V-VI, the pulse duration was increased to 6 ms at the same energy range to reduce the risk of pigmentation changes. It was acknowledged in the patient information leaflet that the desired clinical effect could be reduced by the energy absorption of the competing chromophore of melanin that is increased in darker skin types.

2.5. Excluded treatments

While some treatments (AFL, non-ablative fractional laser (NAFL), micro-needling, scar revision or skin grafting) were not permitted on the study scar, they were permitted for areas of scarring situated in a different anatomical area to the study scar, as defined by head/neck, torso, upper limbs or lower limbs.

2.6. Outcomes

All outcomes, apart from scar colour measurements and observer-rated POSAS, were reported by the participant. Each visit was performed at the respective site. Each participant attended for assessment and treatment at three study visits of 0 (baseline), 6 and 12 weeks, and at the fourth visit for assessment only at the primary endpoint of 6 months. At each assessment, the participant acclimatised for at least 20 minutes to allow skin blood flow and temperature to equilibrate. They remained seated during the assessment.

The primary outcome was patient-rated scar quality (POSAS 2.0 questionnaire, www.posas.org) at 6 months.[19,20] POSAS has been shown to be a valid, reliable and feasible tool for the evaluation of scars. Patient-rated POSAS was captured at each visit. Each of the 6 individual items of POSAS is rated on a 10-point (1−10) score. The total score ranges from 6 to 60, where a higher score implies a worse scar quality. [19]

Secondary outcomes were reported at baseline and primary endpoint of 6 months, unless stated:

1. Blinded observer-rated scar quality (POSAS v2);
2. Patient-rated scar quality (POSAS v2) was also reported at 6 weeks and 12 weeks;
3. Scar colour using a colorimeter (DSM III, Cortex, Denmark).[21] This measured separate values of Erythema (E) and Melanin (M), which were performed three times at each visit, and then averaged for each ROI. For the colour analysis, the difference in measured value of both E & M between the scar and comparison ROIs was used. Higher values of E represent increased (worse) redness or inflammation, and higher values of M represent increased pigmentation. Increased or decreased pigmentation may be an undesirable effect of scarring whereas post-inflammatory hyperpigmentation (PIH) may be an adverse event of caused by PDL treatment;
4. QoL: Assessed and analysed using the burn-specific CARe scale questionnaire (Centre for Appearance Research, Bristol, UK) with 14 subscales;[22]
5. QoL: Further assessed by a short form survey (SF-12, QualityMetric, RI, USA) to calculate Quality Adjusted Life Years (QALYs) using SF-6D.[23] Incremental cost per QALY was then derived from SF-12 using SF-6D;
6. Participant's perception of change in scar quality reported at primary endpoint only. This was a seven-point ordinal response to the question "*In your opinion, what is the overall difference in your 'study scar'?*" ("very much worse", "much worse", "a little worse", "the same", "a little better", "much better" and "very much better"). The measure was dichotomised for analysis into better scar quality (improvement) versus the same/worse scar quality.
7. Healthcare resource use reported at primary endpoint only; captured in two ways. Data on secondary care resource use, for example clinic visits or resource requirements for PDL delivery, were collected using pro-forma. Primary care resource use data (e.g. visits to doctor, and additional personal expenditures, burn care products and travel) were collected using a patient completed questionnaire at primary endpoint. It was assumed that a PDL service was already in place in the cost analysis.

The schedule for the assessments is reported elsewhere.[16]

ELABS also explored patient experience including social and psychosocial impact. A sample of participants (n = 20, ten in each arm) received a telephone interview conducted by an experienced qualitative researcher after the participant completed ELABS.[16] This will be published in a separate article.

2.7. Statistical analysis

No published data were found on the minimal clinically important difference for the patient-reported POSAS to calculate sample size. A one-point improvement on each of the six items, overall change of 6 points, was deemed an important improvement in scar quality by the PPI group. Based on this effect size, the trial required 60 participants in each arm to provide 90 % power, assuming 2-sided 5 % level of significance and a standard deviation of 10. This was increased to 150 participants to account for a 20 % attrition rate.

Analyses were undertaken using statistical software (Stata version 18, Statacorp, Texas, US) and in accordance with the pre-specified statistical analysis plan signed off by the ELABS team and trial steering committee (TSC). Baseline characteristics and outcome data were reported using standard summary statistics. Effect estimates were reported with 95 % CIs and p-values. Significance tests were 2-sided at the 5 % level. Participants were analysed in the arm they were randomised to regardless of whether treatment was completed in keeping with the intention-to-treat principle. The main analyses used a complete case approach. Linear regression was used to compare continuous outcomes between trial arms, reporting the mean difference. Logistic regression was used to compare binary outcomes between trial arms, reporting the odds ratio. Unadjusted analyses and analyses adjusted for study site, burn scar location (head/neck versus torso versus limbs), age, and,

where measured, the baseline outcome score, were undertaken.

Tests of interaction were carried out to compare the intervention effect on the primary outcome across sub-groups defined by scar location and age group (16–24 versus 25–64, versus 65 +). These sub-group analyses were pre-specified in the statistical analysis plan. Additional *post hoc* sub-group analyses were performed to investigate whether the intervention effect differed across subgroups defined by Fitzpatrick skin type: one analysis where the effect for skin type categories I/II/III was compared to that for IV/V/VI and another where the effect for skin type categories I/II was compared to that for III/IV/V/VI.

Several sensitivity analyses were undertaken. A per-protocol analysis of the primary outcome was carried out, excluding intervention arm participants who did not complete any of the three laser treatment sessions. The complier average causal effect (CACE) for the primary outcome, defined as the effect of the intervention in the sub-population of participants that completed all three laser treatment sessions, was estimated with confidence intervals obtained using the bootstrap method. The primary outcome analysis was also repeated including only participants who provided outcome data within two weeks of the date that the 6-month follow-up assessment was due. Finally, analyses of the primary and secondary outcomes were repeated based on analysing multiply imputed datasets. Fifty datasets were imputed using the multivariate normal imputation method. The imputation model included all outcomes at all study waves, trial arms status, the adjustment factors and the auxiliary variable number of laser treatment sessions completed.

A cost-utility analysis (CUA) was conducted from an NHS Personal Social Services (PSS) perspective over the 6-month time horizon. QALYs

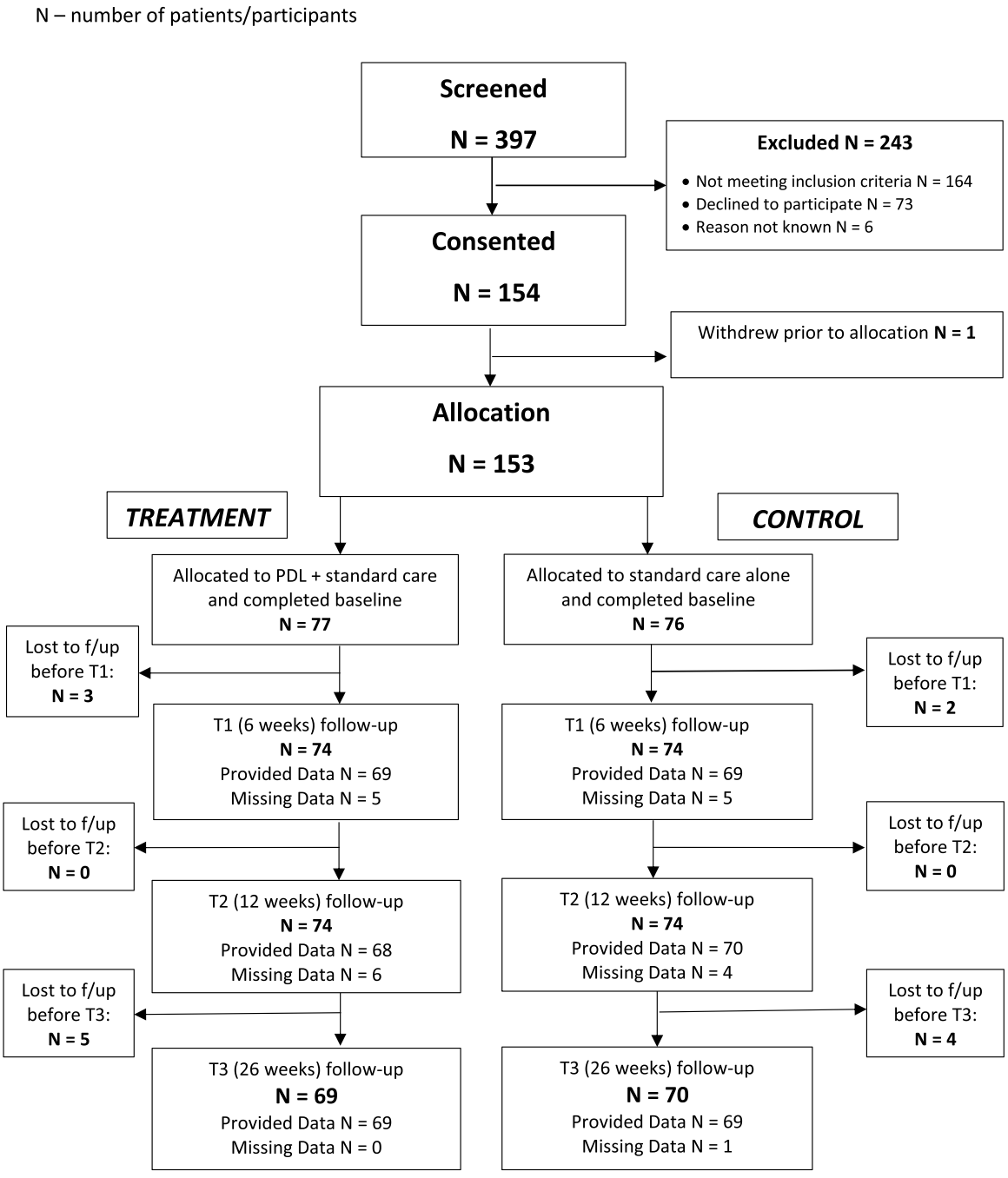

Fig. 1. ELABS CONSORT Flow Diagram. N – number of patients/participants.

were generated using the SF-6D utility algorithm, estimated from SF-12 data collected at baseline and 6 months using an area under the curve approach. Costs were calculated from patient reported resource use and Case Report Forms with a price year of 2022. Differences in costs and QALYs were estimated using seemingly unrelated regression, adjusting for baseline score (SF-6D only), age, gender, scar location and study centre. 95 % confidence intervals were constructed using 5000 bootstrap replications.

A TSC and a Data Safety and Monitoring Committee convened throughout the trial to oversee conduct, change and progress of the study. Trial oversight, database design and data management were provided by a Clinical Trials Unit (ExeCTU, Exeter, UK). The trial was registered with International Standard Randomised Controlled Trial Number registry (ISRCTN14392301).

2.8. Role of the funding source

The funder of the trial had no role in study design, data collection, analysis, interpretation of results, or writing of the report. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR or the Department of Health and Social Care.

3. Results

A total of 153 participants were recruited between Nov 17, 2021, and Jun 30, 2023; 138 were then included in the final complete case analysis (Fig. 1). For the 15 patients who did not complete the study, 11 (7·2 %) were lost to follow-up, three (1·3 %) moved away from area, and one deceased from unrelated illness (0·7 %). Attrition was better than predicted (20 %) at 9·8 % and there were no withdrawals from the study. The dataset was less complete for objective colour measurement (41 in intervention arm, 40 in control arm) with missing data for 57 participants. This was due to cross-infection concerns and technical issues related to the instrument.

The participant baseline characteristics are shown in Table 1. There was a similar distribution between groups in terms of gender, ethnicity, total burn surface area, burn depth, time taken to heal, and Fitzpatrick skin type. The percentage of participants aged 65 + years was twice as great in the intervention group (19·5 % versus 9·2 %). There were only three participants (2 %) with darkest skin types V-VI. There were both more injuries (50 % versus 40·3 %) and fewer chemical injuries (3·9 % versus 14·3 %) in the control group, as well as more burn injuries to the torso in the intervention group (29·9 % versus 18·4 %). A lower initial mean erythema score was seen in the intervention group (7·3 versus 8·4).

The main outcome analysis results are reported in Table 2 for the complete case analyses. Analyses of imputed datasets provided similar results. There was a statistically significant difference for the primary outcome of patient-rated POSAS at 6 months in favour of the intervention arm (adjusted mean difference (AMD) = -4·4; 95 % CI: −8·7 to –0·2; p = 0·041). The findings were similar for the per protocol analysis (AMD = −4·3; 95 % CI: −8·6–0·1; p = 0·054), the complier average causal effect analysis (AMD = −4·5; 95 % CI: −9·9 to −0·3) and the intention-to-treat analysis based on imputed data (AMD = −4·5; 95 % CI: −9·4–0·3; p = 0·068) in supplementary Table S1. When the analysis was restricted to only participants that provided outcome data within two weeks of the scheduled date there was only weak evidence of an effect (AMD = −5·8; 95 % CI: −12·8–1·2; p = 0·104). Tests of interaction indicated little evidence that the effect of PDL on the primary outcome differed across categories defined by scar location (p = 0·627) and age (p = 0·594). The *post hoc* tests of interaction indicated weak evidence that the intervention is more effective for lighter skin types based on the Fitzpatrick classification (p = 0.064 and 0.048); these findings are, however, purely exploratory given they were secondary analyses and not prespecified.

Table 1
Participant baseline characteristics.

Variable/characteristic	Intervention N = 77	Control N = 76	Overall N = 153
Site			
Birmingham, n (%)	4 (5.2)	3 (3.9)	7 (4.6)
Bristol, n (%)	12 (15.6)	13 (17.1)	25 (16.3)
Chelmsford, n (%)	16 (20.8)	17 (22.4)	33 (21.6)
Chelsea, n (%)	13 (16.9)	12 (15.8)	25 (16.3)
Newcastle, n (%)	7 (9.1)	7 (9.2)	14 (9.2)
St Helens and Knowsley, n (%)	9 (11.7)	8 (10.5)	17 (11.1)
Salisbury, n (%)	16 (20.8)	16 (21.1)	32 (20.9)
Gender			
Male, n (%)	38 (49.4)	39 (51.3)	77 (50.3)
Female, n (%)	39 (50.6)	37 (48.7)	76 (49.7)
Age			
16–24, n (%)	8 (10.4)	10 (13.2)	18 (11.8)
25–64, n (%)	54 (70.1)	59 (77.6)	113 (73.9)
65 + , n (%)	15 (19.5)	7 (9.2)	22 (14.4)
Ethnicity			
White, n (%)	63 (81.8)	62 (81.6)	125 (81.7)
Asian, n (%)	7 (9.1)	6 (7.9)	13 (8.5)
Black, n (%)	2 (2.6)	2 (2.6)	4 (2.6)
Mixed, n (%)	2 (2.6)	2 (2.6)	4 (2.6)
Other, n (%)	0 (0)	1 (1.3)	1 (0.7)
Missing, n (%)	3 (3.9)	3 (3.9)	6 (3.9)
Fitzpatrick skin type			
I – Pale white skin	7 (9.1)	6 (7.9)	13 (8.5)
II – White skin	38 (49.4)	34 (44.7)	72 (47.1)
III – Light brown skin	19 (24.7)	22 (28.9)	41 (26.8)
IV – Moderate brown skin	12 (15.6)	12 (15.8)	24 (15.7)
V – Dark brown skin	0 (0)	1 (1.3)	1 (0.7)
VI – Deeply pigmented dark brown to black skin	1 (1.3)	1 (1.3)	2 (1.3)
Cause of burn injury			
Thermal scald	31 (40.3)	38 (50.0)	69 (45.1)
Thermal flame	24 (31.2)	24 (31.6)	48 (31.4)
Electrical	2 (2.6)	0 (0)	2 (1.3)
Thermal contact	5 (6.5)	7 (9.2)	12 (7.8)
Thermal flash	4 (5.2)	3 (3.9)	7 (4.6)
Chemical	11 (14.3)	3 (3.9)	14 (9.2)
Friction	0 (0)	1 (.3)	1 (0.7)
Total burn surface area (percentage), median (IQR)	4 (3–8)	4 (2–9)[a]	4 (2–8)[b]
Time taken to heal in days (clinician report), median (IQR)	50 (34–72)	50.5 (35.5–73.5)	50 (35–73)
Burn depth			
Full thickness, n (%)	32 (41.6)	28 (36.8)	60 (39.2)
Mixed depth, n (%)	22 (28.6)	21 (27.6)	43 (28.1)
Deep dermal, n (%)	19 (24.7)	19 (25.0)	38 (24.8)
Superficial dermal, n (%)	4 (5.2)	7 (9.2)	11 (7.2)
Unknown depth, n (%)	0 (0)	1 (1.3)	1 (0.7)
Size of scar (area in cm2), median (IQR)	160 (75–250)	200 (95–265)	200 (90–250)
Scar location			
Head/Neck, n (%)	3 (3.9)	3 (3.9)	6 (3.9)
Torso, n (%)	23 (29.9)	14 (18.4)	37 (24.2)
Limbs, n (%)	51 (66.2)	59 (77.6)	110 (71.9)
POSAS score – patient report, mean (SD)	43.5 (9.3)	41.9 (10.1)	42.7 (9.7)
POSAS score – observer report, mean (SD)	30.3 (9.9)	31.0 (10.2)	30.6 (10.0)
Erythema score, mean (SD)	7.3 (4.4)[c]	8.4 (4.9)[d]	7.8 (4.7)[e]
Melanin score, mean (SD)	15.8 (6.9)[c]	16.3 (8.0)[d]	16.1 (7.5)[e]

[a] based on 75 participants (pt);
[b] based on 152 pt;
[c] based on 45 pt;
[d] based on 44 pt;
[e] based on 89 pt

There was no statistically significant difference between groups on the secondary outcome of patient-rated POSAS at 6 weeks (p = 0·31) and 12 weeks (p = 0·43). A greater percentage of participants in the intervention arm reported an improvement in secondary outcome of

Table 2
Analysis of outcomes – complete case analysis.

Outcome	Intervention (PDL)		Control (SC)		Unadjusted	Adjusted	
	N	mean (SD) / n (%)	N	mean (SD) / n (%)	mean difference / odds ratio	mean difference / odds ratio (95 % CI)	p-value
POSAS score – patient report at 6 weeks	69	34.4 (11.4)	69	34.6 (11.7)	−0.2	−1.6 (−4.6–1.5)	0.310
POSAS score – patient report at 12 weeks	68	32.1 (11.8)	70	32.8 (12.2)	−0.8	−1.4 (−4.9–2.1)	0.427
POSAS score – patient report at 26 weeks	68	30.4 (13.1)	69	32.6 (13.7)	−2.2	−4.4 (−8.7 to −0.2)	0.041
POSAS score – observer report at 26 weeks	67	22.4 (8.2)	62	21.9 (9.2)	0.5	0.6 (−2.0–3.1)	0.666
Erythema score at 26 weeks	41	4.2 (2.7)	40	3.9 (3.8)	0.4	0.7 (−0.7–2.1)	0.331
Melanin score at 26 weeks	41	10.2 (6.0)	40	10.2 (8.6)	0.006	0.5 (−2.6–3.6)	0.764
Improvement in scar quality (binary) at 26 weeks	68	62 (91.2 %)	69	51 (73.8 %)	3.64	4.44 (1.42–13.9)	0.010
Care Burn Scale at 26 weeks							
Wound/Scar Discomfort	65	7.9 (2.9)	67	7.5 (2.9)	0.4	0.3 (−0.6–1.3)	0.451
Physical Well-being	66	4.3 (1.8)	67	4.5 (1.6)	−0.2	−0.05 (−0.5–0.4)	0.847
Social Situations	65	7.0 (3.9)	68	6.7 (3.5)	0.3	0.4 (−0.8–1.5)	0.550
Friend Support	64	8.7 (3.5)	68	8.9 (3.4)	−0.3	−0.3 (−1.3–0.7)	0.556
Work Life	66	7.4 (2.5)	68	7.0 (2.6)	0.5	0.05 (−0.6–0.7)	0.894
Family Support	66	11.1 (2.8)	68	11.4 (2.5)	−0.3	−0.03 (−0.9–0.8)	0.951
Self-worth	66	8.1 (3.4)	68	8.0 (2.9)	0.05	0.4 (−0.4–1.2)	0.325
Burn Wound/Scar Dissatisfaction	65	4.8 (2.8)	68	4.7 (2.6)	0.08	−0.04 (−0.8–0.8)	0.916
Intimacy/Romantic Relationships	65	8.8 (6.0)	68	8.6 (5.1)	0.2	0.2 (−1.4–1.8)	0.809
Trauma Symptoms	66	13.9 (4.5)	68	14.2 (3.8)	−0.3	−0.2 (−1.3–0.9)	0.689
Negative Mood	65	9.0 (3.3)	68	9.7 (2.4)	−0.7	−0.5 (−1.3–0.3)	0.265
Positive Growth	65	4.8 (2.5)	67	4.6 (2.3)	0.2	0.3 (−0.4–1.1)	0.393

Low scores on POSAS, erythema and melanin indicate favourable outcomes. *High* scores on Care Burn Scale subscales indicate favourable outcomes.

scar quality at 6 months (p = 0·01). There was little evidence of a difference between the groups for the secondary outcomes of CARe QoL subscales (all p-values>0·35), observer-rated POSAS (p = 0·661) and scar colour, both E (p = 0·331) and M (p = 0·764) values.

Missing data for the economic analysis was low. The SF-12 was completed by all participants at baseline and by 90 % at follow-up. Similarly, costs over the 6-month time horizon were calculated for 90 % of participants. Table 3 summarises the SF-6D utility estimates at baseline, 6 months and QALYs. Mean baseline SF-6D scores were similar between trial arms. Examining baseline scores for complete cases, QoL was higher in the control arm than the intervention arm.

At primary endpoint, health-related QoL had increased from baseline in both arms. There was a small difference between arms, favouring the intervention (adjusted mean difference 0·002, 95 % CIs; −0·037: 0·04). The SF-12 Physical Component Summary and Mental Component Summary scores indicated the sample reported their mental and physical HRQL as lower than population norms at baseline. However, at primary endpoint, physical HRQL was similar to the norm in both arms. There were slight differences between arms for both component scores at 6 months and these favoured the control arm.

There was almost no difference in the secondary outcome of QALYs between arms (adjusted difference 0·0004, 95 % CIs −0·0093–0·0102) but the intervention arm had higher costs (adjusted difference £492·76 95 % CIs −320·79–1306·3). The results of the base-case Cost-Utility Analysis (CUA) from an NHS PSS perspective estimated an incremental cost effectiveness ratio (ICER) of £ 1142,808·62 per QALY. The ICER indicates that PDL plus SC is not cost effective compared to SC alone. At a willingness to pay threshold of £ 20,000 per QALY, there is a 12 % chance of PDL plus standard care being cost-effective.

Total NHS and PSS cost was the outcome used in the base-case cost-effectiveness analysis, as shown in Table 4. These were higher in the intervention arm compared to the control arm at 6 months. Mean treatment costs and out of pocket costs paid by participants (e.g. parking, train costs, burn treatments) were higher in the intervention arm, driven by additional laser visits, as seen in Supplementary Table S2. Additional appointments also contributed to higher productivity costs in the intervention arm.

There were 15 adverse events (AEs); 12 in the intervention arm and three in the control arm, as shown in Supplementary Table S3. Additional results are shown in the supplementary Tables S4-S5.

Table 3
Descriptive statistics of economic HRQL outcomes and SF-12 summary scores, where higher scores indicate better quality of life. PCS is the Physical component score and MCS is the Mental component score. Scores above 50 indicate a better-than-average health-related quality of life, while scores below 50 suggest below-average health.

	Control			Intervention		
SF-6D Summary Score	***Mean (SD)***	***Median***	***Range***	***Mean (SD)***	***Median***	***Range***
SF−6D baseline	0.637 (0.132)	0.634	0.372–1	0.636 (0.138)	0.615	0.366–1
SF−6D 26 weeks	0.735 (0.139)	0.723	0.421–1	0.731 (0.163)	0.723	0.373–1
QALYs	0.344 (0.063)	0.334	0.218–0.5	0.340 (0.069)	0.335	0.185–0.5
SF−6D baseline (complete case)	0.641 (0.135)	0.657	0.372–1	0.628 (0.14)	0.602	0.366–1
SF−12 summary score	***Mean (SD)***	***Median***	***Range***	***Mean (SD)***	***Median***	***Range***
PCS baseline	44 (10.1)	44.9	10.6–63.4	43.6 (9.35)	44.8	23.5–62.3
PCS week 26	50.6 (8.5)	53.9	23.9–62	49 (9.67)	51.5	26.8–69
MCS baseline	44.3 (10.8)	44.8	23.4–70.2	43.8 (11.5)	44.6	21.1–64.5
MCS week 26	47.4 (10.1)	47.5	17.3–64.3	47.4 (12.5)	50.0	15.7–66.4

Table 4
Descriptive statistics of costs.

	Control			Intervention		
Costs (£)	***Mean (SD)***	***Median***	***Range***	***Mean (SD)***	***Median***	***Range***
NHS and PSS	1907 (2417)	1139	58–11,916	2465 (2416)	1627	215–14,326
Treatment	310 (358)	194	39–2511	455 (401)	344	48–2624
Out of pocket	203 (249)	135	0–1589	263 (340)	135	0–1774
Productivity	1447 (3795)	16	3.3–21,398	1555 (4070)	35	6.8–20,795
All (societal perspective)	3658 (5053)	1652	72–23,970	4394 (5080)	2601	321–26,798

Table 5
Cost-utility analyses results.

	Incremental cost[a,c]	**Incremental QALY**[b,c]	**ICER (£/QALY)**	**ICER (bootstrapped £/QALY)**[c]	**P1**[d] **£ 20,000**	**P2**[e] **£ 30,000**	**NMB**[f] **£ 20,000**	**NMB**[g] **£ 30,000**
Base case	492.76 (−320.79:1306.3)	0.000 4 (−0.0093:0.0102)	1142,805.70	1142,808.62	0.12	0.13	−489.77	−485.61
Societal perspective	770.79 (−965.50:2507.09)	0.0004 (−0.009:0.0102)	1961,942.10	1961,955.15	0.19	0.19	−714.338	−710.178

[a] Adjusted for age, gender, scar location and site
[b] Adjusted for baseline score, age, gender, scar location and site
[c] Estimates derived from non-parametric bootstrap estimation using 5000 replications
[d] P2 probability of cost-effectiveness at thresholds £ 20,000
[e] P2 probability of cost-effectiveness at thresholds £ 30,000
[f] Net Monetary Benefit at cost-effectiveness thresholds £ 20,000
[g] Net Monetary Benefit at cost-effectiveness thresholds £ 30,000

Table 6
Adverse events.

Adverse event	**Intervention N = 77**	**Control N = 76**	**Overall N = 153**
Overall, n (%)	12 (15.6)	3 (3.9)	15 (9.8)
Blisters, n (%)	2 (2.6)	0 (0)	2 (1.3)
Excessive oedema, n (%)	0 (0)	0 (0)	0 (0)
Pigmentation change, n (%)	3 (3.9)	0 (0)	3 (2.0)
Excessive pain, n (%)	4 (5.2)	0 (0)	4 (2.6)
Scabbing, n (%)	0 (0)	0 (0)	0 (0)
Worsening, n (%)	0 (0)	0 (0)	0 (0)
Wound breakdown, n (%)	1 (1.3)	0 (0)	1 (0.7)
Excessive itch, n (%)	1 (1.3)	0 (0)	1 (0.7)
Skin infection, n (%)	1 (1.3)	0 (0)	1 (0.7)
Unrelated, n (%)	0 (0)	3 (3.9)	3 (3.9)

4. Discussion

ELABS provides evidence that early PDL treatment of HBS is beneficial for improving scar quality, as assessed by patient-rated POSAS outcome. This result was supported by the secondary outcome of participant's perception of change in scar outcome. This concurs with a systematic review regarding treatment of abnormal scars with PDL which concluded that it is superior to conventional modalities for improving overall scar appearance, but comparable when scar parameters were evaluated separately.[24] The use of a patient-rated outcome is susceptible to bias due to the inability to blind the participant to laser treatment, but scar quality impacts the patient's QoL and was deemed important by the PPI group which informed the ELABS study design. The ELABS study design chose an inter-subject comparison of HBS.[16] A limitation of this study was the lack of an intra-subject comparison, which may have both improved internal validity and mitigated variability.

The sample size was calculated based on a mean difference of 6 points between trial arms in POSAS score being clinically meaningful; in the study, the adjusted mean difference was smaller than this (4·4), albeit with a 95 % confidence interval that indicates a larger true difference is plausible. The clinical effect of early PDL treatment may take longer to become apparent as this difference was not seen at 6 nor 12 weeks in ELABS. This effect may further improve with longer follow-up duration than 6 months.

ELABS recruited beyond target with a low attrition rate, contributing to high data collection completeness. A major strength of this study may be attributed to burn scar patients often remaining within the scar management pathway beyond one year and thus low attrition may be expected. This was contrary to previous findings reported in a systematic review of burn studies.[25]

The increased number of older participants (65 + years old) may represent an enrolment bias to this study. Older people tend to scar less severely, this was assumed not to affect the analysis.[26] PDL may be less effective for darkest skin types (V&VI) due to the increased presence of the competing chromophore of melanin.[27] These skin types also have increased risk of AEs, such as permanent pigmentation changes.[28] The limited recruitment meant ELABS was unable to robustly assess either the effectiveness of PDL or the safety profile for this specific sub-group. The population demographic at some sites is a contributory factor here; particularly Salisbury, Essex and to a lesser degree St Helens and Newcastle. Future ELABS studies will aim to address this representation. The similarity in melanin scores from the colorimeter and POSAS between groups shows that post-inflammatory hyperpigmentation (PIH) is not a significant adverse effect of PDL treatment, or that pigmentation caused by the scarring process itself may be a factor.

There were nine adverse events in the laser intervention group, none of these were excessive. Blistering is a rare but self-limiting side effect of PDL treatment of HBS. PIH is a known adverse event from laser, but it is transient.[29] The pain threshold may be lower for this cohort as the wound has only recently healed. No patients withdrew from ELABS for any reason. It is concluded that PDL is a safe treatment for HBS at this early stage of healing for skin types I-IV.

The observer-rated POSAS showed no significant difference for scar quality. This may have resulted either from a lack of observer training or use of different observers at baseline and endpoint, though a inter-rater reliability for this measure of 0·82 is reported.[20] Both the completeness and fidelity of the colour measurement data may have caused the unexpected result of no identified reduction in redness with PDL, where previous studies have observed this effect.[29] The latter as well as the similarity in patient-rated POSAS scores at baseline and primary endpoint for scar colour may imply that reduction in inflammation is

only part of the proposed mechanism of PDL treatment. HBS may be improved as PDL stimulates cytokine and histamine release which remodels collagen.[30]

Early delivery of PDL was not shown to be cost-effective treatment in the relative short-term follow-up of 6 months. It was hypothesised that a shorter-term improvement would serve to "flatten the peak" of scar severity, expedite maturation and lead to an improved scar outcome. It was stated in the study design that 6 months duration was long enough to show any benefits of PDL and short enough to address recruitment and attrition concerns. Given that HBS continues to evolve, the initial improvement in scar quality may result in fewer costs further along in the scar management pathway. The analysis here cannot account for potential long-term savings such as reduced need for future procedures and therapy visits, or productivity losses. A longer-term follow-up than six months is required to fully investigate the effect of PDL as the HBS matures at a duration of up to two years or more, where early PDL may prove its cost-effectiveness.[2]

The study design of enrolment, and ensuing initiation of PDL, at less than 3 months meant that there was variability in duration from wound healing to initiation of PDL. This may have impacted the clinical effectiveness of PDL for each participant, as recent systematic reviews suggest that earlier implementation may be beneficial.[31,32] It is acknowledged that, though the time for initiation of laser was set to within 3 months of wound healing, a sub-group analysis was not included for the correlation between time to initiation of laser and its clinical effect.

ELABS indicates that early PDL treatment of HBS is safe and clinically effective at improving patient-rated scar quality. This is in line with both clinical recommendations, systematic reviews and previous studies.[14, 31–34] Where a PDL service is currently in use, an early PDL treatment protocol for HBS is recommended. Further research is needed to assess the long-term clinical- and cost-effectiveness of early PDL intervention.

Ethics Committee approval

Ethics was approved by the NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW) in the United Kingdom. REC Reference 21/SW/0049.

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Declaration of Competing Interest

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Contributors

MB, SD, and JP designed the study. MB, SD, VH and SR planned the study. MB, SD, VH, SR, OU, KB, KA, and NB-F implemented the study. MB, VH, JP, KB, KA, KS, QF, and CL collected the data. SD, OU, KB, and NBF analysed the data. SD, OU, and KB interpreted the data. SD & OU created the data visualisations. MB wrote the first draft and manuscript revisions. MB, SD, VH, OU, JP, KB, KA, NB-F, KS, QF, and CL reviewed and edited the manuscript. All authors had full access to all the data in the study, read and approved the final version of the manuscript, and had final responsibility for the decision to submit for publication. SD and OU directly accessed and verified the underlying data reported in the manuscript.

Data Sharing

Access to shared (de-identified) data will be via the trusted data repository, Researchfish (Elsevier) and will be linked from institutional repositories. Data is supported by relevant documentation such as the data dictionary, study protocol, statistical and health economics analysis plan.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2025.107500.

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