Secondary intention wound healing following excision of keratinocyte cancers on the lower leg (HEALS2): draft protocol synopsis

Background

The number of people with skin cancer is increasing due to demographic changes and social behaviours. Our patients are an aged population and high post-operative complication rates are reported in this very elderly patient population. While postoperative compression therapy is currently used for some patients after skin surgery to the lower leg, there is variation in practice and clinical equipoise exists so there is an opportunity to evaluate this 'simple' intervention.

Keratinocyte cancers (KC) including basal cell and squamous cell carcinomas are very common (incidence 245.1/100 000 or 210,000 diagnosed annually) but have high cure rates with surgical excision and primary closure/skin graft/flap or partial/no closure and healing by secondary intention.

Surgical wounds healing by secondary intention (HBSI) after excision of KC lesions on the lower leg (approximately 12% of all KCs) provide particular clinical challenges. First, due to anatomical location and lack of skin laxity, many are not amenable to primary closure or local flaps. Second, people undergoing surgery for KC on the lower leg are typically elderly with concurrent mobility limitations, peripheral vascular/venous disease and local oedema, factors which delay healing and increase risk of complications including infection. Third, post-operative oedema due to the inflammatory process is a common sequela of surgical wounds which normally resolves within a few days in most body sites. However, in the lower leg, the cumulative effect of peripheral vascular/venous disease and gravity delays this resolution and is likely to compromise wound healing.

Compression therapy has been established by primary research/systematic review evidence as the primary/first line treatment strategy for healing of venous leg ulcers and also informed which compression systems are most effective. Compression is now in common clinical use for the treatment of venous leg ulcers and has transformed venous leg ulcer management, reducing the burden of wounds.

Mechanistically compression reduces oedema and improves venous return and tissue oxygenation. Given the high levels of underlying venous disease and the normal occurrence of post-operative oedema due to the inflammatory process it is proposed that lower leg surgical wounds HBSI may benefit from compression in a similar manner. However, it is also recognised that compression therapy can be resource intensive (although the use of compression hosiery is now enabling patient self-care) and can sometimes be difficult to apply and be uncomfortable for the patient. When our patient group were presented with different compression options, most members agreed that bandages might be hot and/or uncomfortable but those who had experienced oedema/infection or delayed healing were less concerned with these issues. It is therefore essential to assess the clinical and cost effectiveness of compression as a primary post-operative intervention in terms of reduced time to healing and secondary outcomes including infection.

Aim and objectives

Aim: The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost effectiveness of compression therapy in the healing of surgical wounds healing by secondary intention (HBSI) following excision of lower limb keratinocyte cancers (KC).

Primary objective: The primary objective is to compare the time to healing from randomisation, between standard care or standard care plus compression therapy.

Secondary objectives: Secondary objectives will compare groups for

- Incidence of infection as measured by adapted Bluebelle Wound Healing Questionnaire (WHQ) until healing
- Number of days participants are prescribed antibiotics until healing
- Scar quality as measured by Patient and Observer Scar Assessment Scale (POSAS)
- Safety events including related complications and hospitalisations to 12 months post randomisation
- Cost effectiveness via a within-trial and decision analytic model assessed from a payer perspective measuring patient health related quality of life in Quality Adjusted Life Years (QALYS) meeting updated CHEERS 2022 updated reporting guidance
- Resource use and Health-related quality of life as measured by EQ-5D-5L to 12 months post randomisation.
- To determine the relationship between partial wound closure, wound area, and time to healing

Exploratory objectives:

- Explore associations between wound area reduction between baseline and 4 weeks post randomisation and time to healing
- Explore patient acceptability and factors affecting adherence to randomised treatment

Qualitative sub study objectives:

- Challenges and difficulties encountered during CT
- Impact CT has on daily activities and quality of life
- Patients' satisfaction with the support provided
- Factors influencing patients' decisions to continue or discontinue CT

Trial design

The trial is a multicentre, prospective, Phase III, parallel group, open-label, randomised, controlled trial with embedded internal pilot, blinded endpoint assessment, economic evaluation, minimum 6-month/maximum 12-month follow-up comparing time from randomisation to complete surgical wound healing (epithelialisation) between control (standard care - SC) and intervention (standard care plus compression therapy - CT) groups.

Randomisation will take place immediately post-operatively (in theatre or post-operative recovery area). 396 participants will be randomised in a 1:1 allocation ratio (198 per group) to SC or CT using a minimisation algorithm stratifying by

- Centre
- Immediate post-excision wound area (prior to any partial closure 6.0cm^2 or less/more than 6.0cm^2)
- Wound depth (excision to fat/excision to fascia or periosteum)

Randomisation will be performed via a central, independent, secure 24-hour automated randomisation system provided by Leeds CTRU using a minimisation algorithm (including a random element) to ensure allocation concealment.

Participants will be recruited from UK centres which offer skin cancer surgery services (SCSC) including district general and teaching hospital settings.

Internal pilot

In line with funder requirements the trial monitoring includes an internal pilot. Details of this are incorporated into the TSC/DMEC statistical monitoring plan, with timelines revised as necessary by the TSC/DMEC and funder.

Trial flow diagram