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Intralesional cryotherapy versus excision with corticosteroid injections or brachytherapy for keloid treatment: Randomised controlled trials

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Summary *Background:* Keloids are a burden for patients due to physical, aesthetic and social consequences. Treatment remains a challenge due to therapy resistance and high recurrence rates. The main goals of treatment are to improve scar appearance and symptoms and patients' quality of life (QoL).
Methods: Two multicentre, randomised controlled open trials that compared 1) intralesional cryotherapy with excision and corticosteroid injections for primary keloids, and 2) intralesional cryotherapy with excision and brachytherapy for therapy resistant keloids. Primary outcome was scar appearance assessed with the Patient and Observer Scar Assessment Scale. Secondary outcomes were patient reported QoL (Skindex-29, SF-36, EQ-5D-5L), recurrence rates and scar volume reduction. For analysis, a linear mixed model was used. Power analysis indicated 33 patients in each group were needed.
Results: The trial was prematurely terminated after inclusion of 26 patients due to unexpectedly inferior outcomes after intralesional cryotherapy. For primary keloids no convincing

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difference between treatments was found, but surgery improved scar appearance while cryotherapy did not. For resistant keloids, excision followed by brachytherapy improved scar appearance (POSAS) and scar symptoms (itch and pain) significantly ($p < 0.001$, $p < 0.001$ and $p = 0.006$ respectively) while cryotherapy did not. Neither of the treatments caused indisputable improvements in QoL.

Conclusions: Intralesional cryotherapy is inferior to keloid excision followed by brachytherapy for resistant keloids. In primary keloids, intralesional cryotherapy reduced keloid volume and, therefore, may be used in these patients and specific cases. Primary keloid group size was too small to draw valid conclusions, further research on the efficacy of intralesional cryotherapy for primary keloids is warranted.

Background

Keloids cause a burden on health related quality of life that justifies adequate treatment.[1,2] Both patients and physicians are challenged due to therapy resistance and keloid recurrences. Current opinion is that treatment should follow a stepped care approach from conservative, non-invasive treatment to surgical treatment followed by adjuvant treatment in case of unsatisfactory results.[3,4] In 2003 a new application of cryotherapy for treatment of keloids was introduced by Har-Shai et al.,[5] after which no recurrences were reported. Also, in several other studies equally promising and remarkable results were found for both primary and recurrent keloids,[6–8] suggesting this treatment could replace surgical treatment.

Intralesional cryotherapy previously had not been compared directly to other treatments, hence we designed a randomised controlled trial to compare outcomes of intralesional cryotherapy to excision and adjuvant treatment, starting in 2012.[9] Since the start of our trial three studies have been published on intralesional cryotherapy, which showed results inferior to the first reports, however, outcomes were still reasonable with recurrence rates of 12%, 17%, and 24%.[10–12]

After keloid excision several adjuvant treatments are available, of which corticosteroid injections and radiotherapy (external of brachytherapy) are often used. The biggest disadvantages of corticosteroids are atrophy of the scar or surrounding soft tissues and the remaining recurrence risk of 10%–40%.[13] A more aggressive adjuvant treatment is radiotherapy which has lower recurrence rates of 5%–25%,[14,15] but it also has several important disadvantages. Radiation impairs wound healing which is necessary after keloid excision and it can cause dermatitis, fibrosis and telangiectasias. Radiation inhibits keloid recurrence by causing DNA damage to the fibroblasts. This adds to the cumulative tissue damage throughout life, thereby raising the occurrence of malignancies years after treatment. Reports on malignancies caused by keloid related radiation are sparse, but patients should be informed about this issue and long term follow-up is recommended.[16]

During the course of the present trial, patient inclusion was difficult and we unexpectedly encountered strikingly inferior outcomes following cryotherapy. Therefore, after careful consideration we decided to stop further enrolment of the trial. In the current report we present the results of this terminated randomised controlled clinical trial.

Methods

A randomised non-blinded clinical trial was designed to compare intralesional cryotherapy to extralesional keloid excision followed by adjuvant treatment divided in two groups:

- For primary keloids (not previously treated with surgery) we compared intralesional cryotherapy to excision followed by adjuvant triamcinolone acetonide injections.
- For resistant keloids (recurrence after previous surgical treatment or refractionary to corticosteroid injections) we compared intralesional cryotherapy to excision followed by brachytherapy.

Adult patients were eligible if they had a burdensome keloid that had not responded well to minimally invasive treatment and, therefore, had an indication for excision. Keloids had to be minimally 1 by 1 cm, and feasible for primary closure after excision. The trial started at two University Medical Centres, during the trial two other centres were added. Treatment allocation was conducted through a central computerised allocation. The trial was registered (Dutch Trial Register NTR 4151) and approved by the local IRB (MEC 2012-212), all patients gave written informed consent.

Treatments

Excision with additional corticosteroid injections: Extralesional excision was performed with minimal margins. After 2 weeks, an injection of triamcinolone acetonide 40 mg/ml was given in the newly formed scar. If needed, the injections were repeated at 8 and 12 weeks postoperatively.

Excision with additional brachytherapy: Extralesional excision was performed with minimal margins. During the procedure, brachytherapy catheters were placed subcutaneously in order to cover the affected area. A target dose of 9 Gy was given followed by a second dose on the same day. After completion of brachytherapy, the catheter was removed.