Drug-free microneedles in the treatment of keloids: a single-blinded intra-individual controlled clinical trial

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Keloids are a common skin disorder with significant morbidity. Itch and pain are common symptoms that affect up to 80% of patients [1]. First-line treatment is repeated intra-lesional corticosteroid injections which is painful and prone to recurrence [2]. In a previous study, we observed that solid microneedles exhibited contact-dependent inhibition on cultured keloid and normal skin fibroblasts, in the absence of drugs [3-4]. We aim to develop a minimally-invasive, drug-free, self-administered treatment for patients who are not suitable for other forms of therapy. The aim of this trial is to determine the efficacy and safety of continuous application of these microneedle patches in the treatment of keloids.

The study was a single-blinded intra-individual controlled trial of eight-week duration. In each subject, two keloids one-two cm in size were identified. The keloid most easily accessible to the patient was allocated to the microneedle-treatment arm while the other to the non-interventional control arm.

To apply the microneedle patch, the subject sterilizes the skin surface using an alcohol swab, places the microneedle patch on the keloid, and secures the patch with a water-proof dressing. Application was continuous throughout the treatment duration with extra microneedle patches provided for re-application in event of dislodgement. Subjects were evaluated at the end of four weeks and eight weeks.

Evaluations were performed at baseline (Visit One), after four weeks of treatment (Visit Two) and after another four weeks of non-treatment (Visit Three). Primary outcome measure was the mean keloid volume determined by a high-resolution three-dimensional scanner. Secondary measures were self-assessment of average pain and itch experienced in the prior one week and the Vancouver Scar Scale (VSS) administered by a blinded evaluator [5].

Twenty-eight patients, 24 males and four females were recruited. One patient defaulted without starting treatment and 27 patients completed the study. After four weeks of treatment, the mean

keloid volume reduced significantly from 218.2mm^3 to 195.6mm^3 (p=0.001), a 10.4% reduction. This change was significantly greater than that of controls (p<0.001). After the subsequent four weeks without treatment (Visit Three), the mean volume of the keloids significantly increased back in size to 212.6 mm^3 (p=0.014). [Table 1]

Treated keloids were significantly less painful after four (p=0.038) and eight (p=0.01) weeks compared to baseline. Treated keloids were significantly less itchy after eight weeks compared to baseline (p=0.002). The mean VSS score for treated keloids was significantly reduced after four weeks of treatment compared to baseline (p=0.007), but this was not significantly different compared to controls. The subjects tolerated the microneedles well with no adverse events reported. Eighteen (66.7%) subjects preferred the microneedles treatment method over their previous intra-lesional injections mainly due to lesser pain and increased convenience.

In our previous laboratory studies [6], we found that drug-free solid microneedle in contact with fibroblast cultures over a 12-hour period induced fibroblast cell death and significantly increased the number of non-viable fibroblasts compared to control. Application of the microneedles on part of a post-surgical hypertrophic scar in a volunteer induced a reduction in size, redness and itch in the treated portion [6]. We next tested the effect of applying just the bare backing of the microneedle patch on a volunteer with keloids (the microneedles were filed away) – there was no reduction in keloid size observed, indicating that pressure of application alone did not result in reduction of keloid size.

We hypothesize that microneedles disrupt the interactions between the dermal fibroblasts and their surrounding collagen and other fibroblasts, resulting in regression of the fibroblasts and consequent reduction of collagen production and keloid volume. Further studies are needed to determine the exact mechanisms of this phenomenon. The increase in keloid size after stopping treatment, approaching that of the baseline, indicates that the intervention was effective. The optimal duration of microneedle application to achieve efficacy, while minimising inconvenience, is uncertain and

more studies are needed to determine this. Other limitations include that adherence was self-reported and compliance may not be accurate.

The microneedle patches were much less painful than conventional steroid injections. They are also drug-free and serve as an alternative for the increasing number of steroid-phobic patients. Self-administration of the microneedles greatly reduces the need of frequent visits to the clinicians and thereby incurs much lower healthcare costs. The microneedles can also be fabricated in a customised manner to fit the greatly varied sizes and shapes of different keloids.

In conclusion, the results demonstrated that continuous application of drug-free microneedles significantly reduced the volume and associated pain and itch of keloids.

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Table 1: Size of keloids (mm^3) at each visit comparing control (non-intervention) and microneedle-treated keloids in 27 subjects

Size of keloids (mm^3)	Visit 1	Visit 2	Visit 3	Change from Visit 1 to 2	Change from Visit 2 to 3	Change from Visit 1 to 3
Control keloids						
Mean ± SD	148.6 ± 204.4	155.7 ± 221.9	155.8 ± 223.9	7.2 ± 25.7	0.05 ± 11.7	7.2 ± 29.0
Median (min, max)	49.3 (2.5 , 855.0)	44.0 (1.5 , 979.0)	48.0 (2.5 , 1001.0)	0.7 (-23.7 , 124)	-0.33 (-29.7 , 24.7)	0.3 (-11.3 , 146)
p-value for comparing visits within the control group				0.104	0.983	0.101
Microneedle-treated keloids						
Mean ± SD	218.2 ± 329.6	195.6 ± 292.5	212.6 ± 317.0	-22.5 ± 49.2	17.0 ± 38.8	-5.6 ± 22.9
Median (min, max)	117.0 (10.3 , 1592.0)	132.3 (5.2 , 1422.7)	114.7 (10.7 , 1549.7)	-9.7 (-169.3, 83.3)	7.0 (-94 , 127)	-1.7 (-66.3 , 34.7)
p-value for comparing visits within the microneedle group				*0.001*	*0.014*	0.405
p-value for comparing visits between the microneedle and control groups				*<0.001*	*0.024*	*0.007*

Note: Size of keloids (mm^3) was based on the mean of 3 measurements per keloid.