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Microneedles assisted incubation during aminolevulinic acid photodynamic therapy of actinic keratoses - a randomized controlled evaluator blind trial

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Dear Editor,

Photodynamic therapy (PDT) is a common method of treating actinic keratoses (AKs) that compares favorably to other treatment methods.[1,2] However, treatment is limited by prolonged incubation times required for the medication to penetrate the stratum corneum. [3]

Microneedles (MNs) are micrometer scale needles that are capable of puncturing the stratum corneum with minimal pain.[4,5] They have been utilized for various applications, including enhanced drug delivery.[6] Few studies have evaluated MNs in conjunction with PDT for AKs.[7]

We sought to assess the utility of short solid MN arrays that penetrate to the epidermis in shortening the incubation time for aminolevulinic acid (ALA) in PDT for AKs. To this end we undertook a prospective, single-blind, split-face, rater-blinded, randomized, sham-controlled, non-inferiority trial with 51 participants. MNs and sham pretreatments were randomized on the right and left foreheads and the sham treated sides were incubated with 5-ALA for 60 minutes which is the standard at our medical center. MN pretreated sides were further randomized to 20, 40, or 60 minute 5-ALA incubation. The primary outcome was complete response rate (CRR) of AKs at one month after treatment. Secondary outcomes were post MN treatment and post PDT treatment pain. A priori power analysis revealed that at least 15 subjects would allow greater than 90% power to discern a change in 1 AK between the right and left forehead with $\alpha = 0.05$ with a Wilcoxon signed-rank evaluation of matched pairs.

The MN device (Microchannel Skin System,® 3M Company, St. Paul, MN) consisted of an array of microneedles that were 690 micrometers in length. The sham treatment consisted of the applicator without actual microneedles. 5-ALA (Levulan® Kerastick®, Dusa pharmaceuticals® Wilmington, MA, USA) was applied to the entire face. At the end of the incubation period, subjects were exposed to blue light (Blu-U®, Dusa pharmaceuticals® Wilmington, MA, USA) with a wavelength of 417 nm ±5nm, for 8 minutes for a total fluence of 4.8 J/cm^2.

Forehead AKs were mapped prior to any intervention. The subjects were asked to rate the pain immediately after pre-treatment with the MNs and sham device and also following blue light treatment by marking their level of pain on a 100 millimeter (mm) visual analog scale (VAS)[8].

All subjects returned four weeks after initial treatment for a follow up evaluation visit. Mapping of lesions was performed by two different evaluators. The primary outcome was complete response rate (CRR) defined as the difference between the lesion count in the first and second visit normalized to the baseline count.

Statistical analysis was performed using a paired Student t-test, Wilcoxon ranked sign test and analysis of variance as appropriate. Data was tested for normality using Shapiro-Wilk test. All analyses were conducted using R Studio® (RStudio, Inc. Boston, MA, USA) and Excel® (Microsoft Corporation, Redmond, WA, USA). A p value < 0.05 was considered statistically significant.

Ninety-four patients were screened to enroll our target of 51 subjects (figure 1A). A total of 48 and 47 subjects completed all study endpoints for pain and AKs counts

respectively. Our study population was predominantly male, older in age (average age 67.7 years and range 49-86) and 100% had Fitzpatrick skin type 2[9] (Table 1). Average CRR (SEM) for the 20, 40 and 60 minute MN incubation times versus the corresponding sham MN treatment with 60-minute incubation were 71.4% (5.8) & 68.3%(3.3); 81.1% (4.6) & 79.9% (4.5); and 72.1% (5.5) & 74.2% (6.9) respectively (table 1). There were no statistically significant differences in efficacy between the microneedle and sham device treatments (figure 2C). Average pain scores after MN pretreatment (SEM) in the treatment and sham arms were 13.1 (2.6) & 2.4 (0.5) mm respectively (N=48, $p<0.01$), (see figure 2D). Average pain scores after PDT light treatment (SEM) in the 20, 40 and 60 minutes treatment and control arms were 15.7 (4.9) & 17.7(4.9); 26.4 (7.5) & 24.7(7.1); and 37.2(6.6) & 26.0(4.9) mm respectively ($p=0.35$; $p=0.23$; $p=0.046$) , (figure 2D). No adverse events were reported.

Our primary findings suggest that MN devices may reduce incubation periods required for PDT, while maintaining equivalent efficacy to the standard one-hour incubation time used in our clinic.

Other studies have investigated the use of MNs in combination with PDT for the treatment of AKs however longer MNs were used and resulted in dermal injury which may increase patient discomfort and lead to bleeding and increased adverse events.[7,10] This randomized controlled trial is distinct in that it used MNs that only reach the epidermis.

Though we found a statistical significance in pain scores between MN application and the sham device, the difference was relatively minor.

To our knowledge this is the first assessment of the effects of short ALA incubations in PDT to human skin with AKs. Interestingly efficacies were similar in the 20, 40 and 60 minute MN arms.

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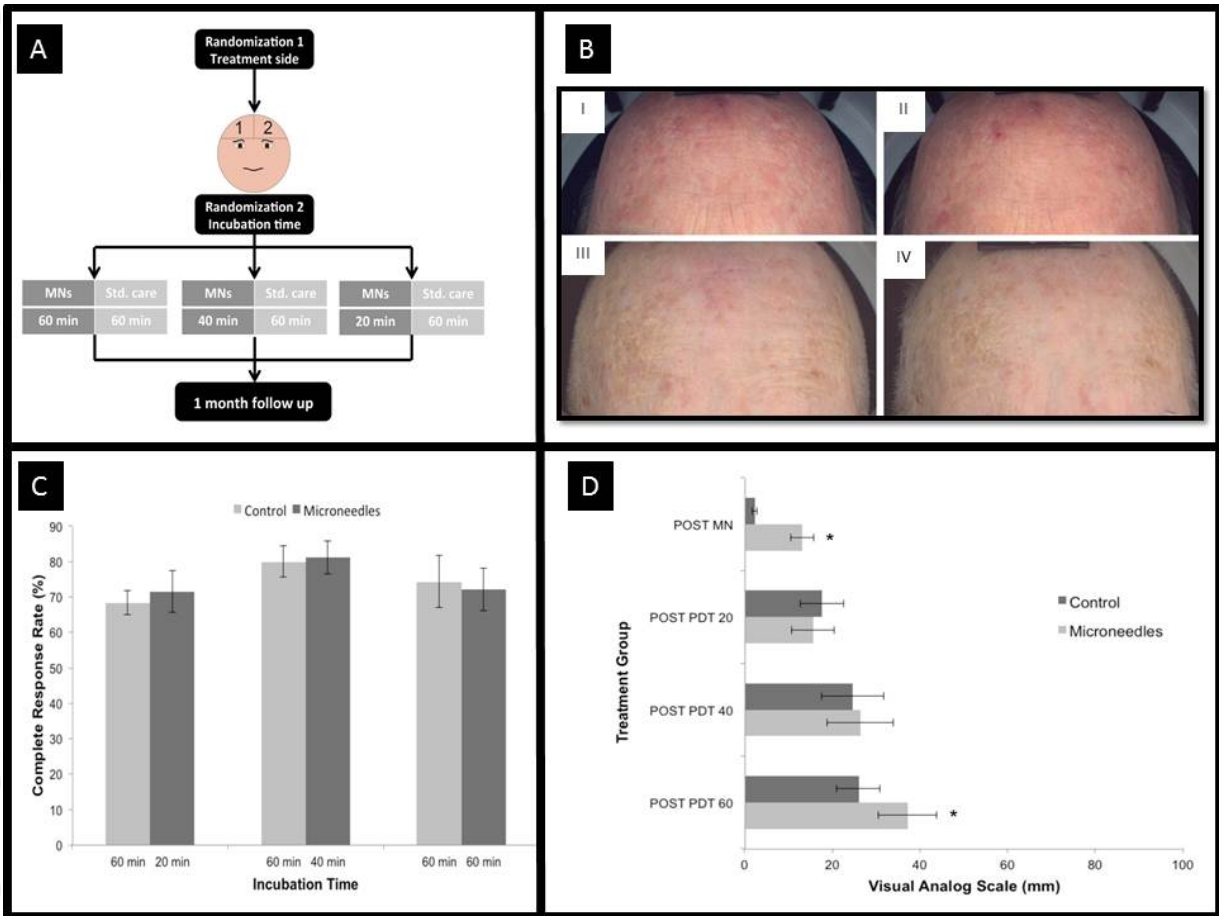

Figure 1. A) Study flow schematic. MNs – microneedles, min – incubation minutes. **B)** Forehead view of actinic keratoses before (I and III) and one month after (II and IV) PDT treatment with microneedle pretreatment (subjects' left forehead in all images) and with sham pretreatment (subjects' right forehead in all images). **C) Actinic keratosis complete response rate results.** Average CRR (SEM) for the 20, 40 and 60 minutes treatment and control arms were 71.4% (5.8) & 68.3%(3.3); 81.1% (4.6) & 79.9% (4.5); and 72.1% (5.5) & 74.2% (6.9) respectively (N=15, p=0.51; N=16, p=0.79; N=16, p=0.72). **D) Pain scoring after microneedle application.** Pain assessment using a 100 mm visual analog scale (VAS) was performed after microneedles (MN) pretreatment and after photodynamic therapy in all treatment groups (PDT 20 – 20 minutes ALA incubation, PDT 40 – 40 minutes ALA incubation, PDT 60 – 60 minutes ALA incubation). Average pain scores after MN pretreatment (SEM) in the treatment and control arms were 13.1 (2.6) & 2.4 (0.5) mm respectively (N=48, p<0.01). Average pain scores after PDT light treatment (SEM) in the 20, 40 and 60 minutes treatment and control arms were 15.7 (4.9) & 17.7(4.9); 26.4 (7.5) & 24.7(7.1); and 37.2(6.6) & 26.0(4.9) mm respectively (N=15, p=0.35; N=16, p=0.23; N=17, p=0.046). * = $p < 0.05$; ** = $p < 0.01$.

Treatment group by incubation time	20 min	40 min	60 min
Total participants, N	15	16	17
Gender M / F	12 / 3	15 / 1	13 / 4
Average Age, Years (SEM)*	70.2 (1.7)	66.9 (2.5)	66.2 (2.5)
Average time between treatments, Days (SEM)*	30.9 (1.6)	27.8 (0.8)	28.3 (1.3)
Total AKs analyzed (n)	108	109	98
Before PDT mean AK count			
MN side (SEM)	7.2 (0.8)	6.8 (0.6)	6.3 (0.6)
Control side (SEM)	7.3 (0.8)	8.4 (0.9)	6.9 (0.5)
After PDT mean AK count			
MN side (SEM)*	2.3 (0.5)	1.4 (0.4)	1.9 (0.4)
Control side (SEM)	2.3 (0.4)	1.6 (0.4)	1.8 (0.4)
Change in mean AK count			
MN side (SEM)*	4.9 (0.6)	5.4 (0.5)	4.4 (0.5)
Control side (SEM)	5 (0.6)	6.8 (0.8)	5.1 (0.6)
Complete Response Rate (%)			
MN side	71.4	81	72.1
Control side	68.3	79.8	74.2

Table 1. Study participants and mean absolute lesion counts. Total lesions analyzed = 663. SEM = standard error of the mean; PDT= photodynamic therapy; SEM – standard error of the mean. * $p>0.05$