

Clinical Assessment of AK following Levulan and BLU-U Photodynamic Therapy after Pre-treatment with a Sterile, Plastic Microneedle Device (MSS™)

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Abstract

A small-scale clinical study was conducted wherein the use of a sterile, plastic microneedle device (Microchannel Skin System – MSS™) was investigated for pretreatment prior to photodynamic therapy for the treatment of actinic keratosis (AK) lesions. Over the 30 day study, lesions that were pretreated with the MSS were cleared at a significantly higher rate than those that were not pretreated with the MSS. MSS pretreatment of AK lesion may enhance photodynamic therapy by increasing the absorption of the photosensitizing agent prior to blue light treatment.

Background

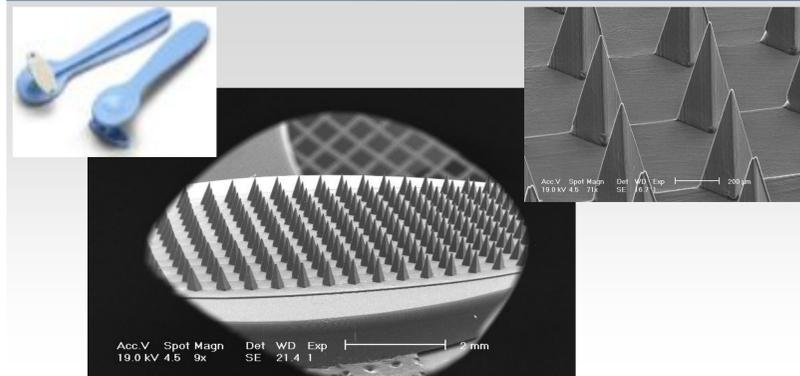
3M has produced polymeric microneedle arrays that, when applied by hand, disrupt the stratum corneum and epidermis creating microchannels in the skin. Testing was conducted to characterize the microchannels, test the durability of the microneedles, and demonstrate enhanced delivery of topically applied formulations of lidocaine hydrochloride and methylprednisolone.

3M's Microchannel Skin System (MSS) arrays were applied to domestic swine using controlled forces to demonstrate reliability of penetration, depth of penetration (DOP), and durability of the microstructures to repeat application under both normal and high force. Tissue levels of lidocaine and methylprednisolone following topical application with and without microneedle pretreatment were determined by HPLC-MS analysis following digestion of biopsies.

Results indicated nearly all microneedles penetrated the stratum corneum upon hand force application. The DOP varied from <100µm to nearly 150µm depending on the application force and the firmness of the underlying tissue. The arrays showed excellent durability to repeated *in-vivo* application, with less than 5% of the structures evidencing even minimal tip bending after 16 applications.

A lidocaine hydrochloride formulation applied topically *in-vivo* showed ~340% increase in local tissue levels when the MSS arrays were used to twice pre-treat the skin prior to applying the drug. Local delivery of a topically applied formulation of methylprednisolone was over one order of magnitude higher when the application site was twice pre-treated with the MSS array.

MSS Array



Completeness and Depth of Penetration, Hand application of the MSS array

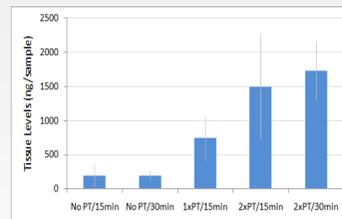
Penetration for arrays vs application force to firm or soft tissue, n=3

	1.2 – 1.4 lbf	3 lbf	5 lbf
Firm Tissue, Avg ± SD	82 ± 6%	95 ± 4%	92 ± 11%
Soft Tissue, Avg ± SD	48 ± 34%	84 ± 7%	99 ± 2%

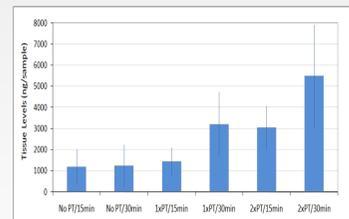
Average in-vivo DOP for square arrays vs application force to firm tissue (rib area), n=3 applications with 66 measurements/application

Application Force	2 lbf	3 lbf	5 lbf
Average DOP (n=3)	85µm	100µm	138µm
SD	4.6µm	18.0µm	12.7µm
%RSD	5.4%	18.1%	9.3%

Local Tissue Concentrations of Methylprednisolone and Lidocaine following Application and Pretreatment with the MSS



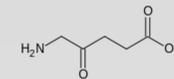
Tissue levels of methylprednisolone following formulation application on skin that was not pre-treated with an MSS array, pre-treated one time with an MSS array or pre-treated two times in succession with an MSS array. Application time of the formulation, indicated on the graph, was either 15min or 30min.



Tissue levels of lidocaine following formulation application on skin that was not pre-treated with an MSS array, pre-treated one time with an MSS array or pre-treated two times in succession with an MSS array. Application time of the formulation, indicated on the graph, was either 15min or 30min.

MSS Pre-treatment for AK

In a clinical study, three subjects with at least 10 AK lesions distributed with at least 5 lesions on each side of the face, were presented for photodynamic therapy with Levulan® (aminolevulinic acid, 20% solution).



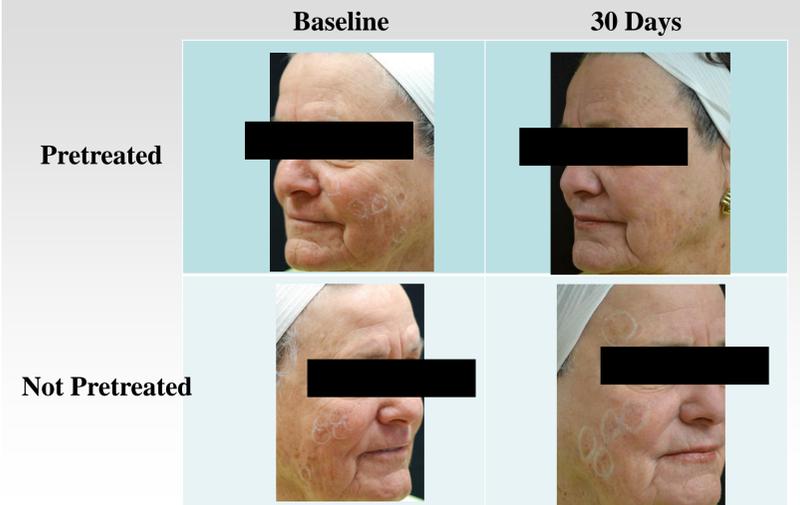
On Day 1, an AK count was conducted. The left side of each subject's face was pretreated with the MSS device immediately prior to application of Levulan®. The right side of the face was not pretreated prior to Levulan® application.

After 1 hour (typical treatment time is 6 – 24 hours), the subject's faces were cleansed and placed in a Blue Light Photodynamic Therapy Illuminator (BLU-U). Subjects returned for reassessment on Day 30 following treatment and the AK count was repeated.

AK Count (Initial and 30 Days) for subjects treated with photodynamic therapy with and without MSS pre-treatment

Subject	Side	Pre-treat	Number of Lesions		
			Initial	30 Days	% Clearance
1	Left	MSS	7	1	86%
	Right	None	6	5	17%
2	Left	MSS	5	1	80%
	Right	None	7	4	43%
3	Left	MSS	10	0	100%
	Right	None	10	6	40%
Total	Left	MSS	22	2	91%
	Right	None	23	15	35%

Before and After (Initial and 30 Days) Images of AK Lesions



Conclusions

The Microchannel Skin System (MSS) is the first microneedle product launched from 3M's Microstructured Transdermal System (MTS) platform.

The MSS array demonstrates consistent penetration of the stratum corneum with as little as 1.3 lbf applied by hand. The depth of penetration varies from about 80 – 150µm depending upon the force of application and upon the firmness of the underlying tissue.

MSS pretreatment creates hydrophilic channels in the skin. Following pretreatment with the MSS device, some drug formulations may be absorbed faster or to a greater extent than when they are applied to skin without microchannels.

Clinical study results indicate the potential for pretreatment of the skin with the MSS to enhance the therapeutic effects of photodynamic therapy for the treatment of AK.

References

Duan, D., Moeckly, C., Gysbers, J., Novak, C., Prochnow, G., Siebenaler, K., Albers, L., Hansen, K., 2011. Enhanced delivery of topically-applied formulations following skin pre-treatment with a hand-applied, plastic microneedle array. *Curr. Drug Deliv.* 8, 557-565.

Hoesly, F., Borovicka, J., Gordon, J., et al., 2012. Safety of a Novel Microneedle Device Applied to Facial Skin. *Arch Dermatol.* Published online March 19, 2012, doi: 10.1001/archdermatol.2012.280.

