Original Article

Safety and efficacy of a novel robotic, fractional micro-coring device in a swine model

Yuval Ramot[1,2], Udi Vazana[3], Orna Cacical[3], and Abraham Nyska[4,5*]

[1] Faculty of Medicine, Hebrew University of Jerusalem, Campus Ein Kerem, Jerusalem 9112102, Israel
[2] Department of Dermatology, Hadassah Medical Center, Campus Ein Kerem, Jerusalem 9112102, Israel
[3] LAHAV CRO, Kibbutz Lahav, Israel
[4] Consultant in Toxicologic Pathology, Yehuda HaMaccabi 31, Tel Aviv 6200515, Israel
[5] Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel

Abstract: Laser resurfacing may be accompanied by unwanted side effects. The micro coring technology, designed to remove small skin columns, was developed to avoid the thermal injury associated with lasers. However, very limited data are available on its preclinical efficacy and safety. The novel robotic, fractional micro-coring device, Aime™, was tested on four pigs, each treated in 12 sites, at 6 time-points, over the course of 28 days. Macroscopic and microscopic evaluation was performed at each of the 6 time-points during the 28-day follow-up. Macroscopically, treatment resulted in erythema and mild edema that quickly resolved. Microscopically, there was progressive re-coverage of the tested sites with complete, well differentiated, newly formed epidermis, associated with efficient elimination of the underlying excised dermis, which was replaced by maturing fibroplasia. Some of the sites demonstrated complete healing already after 7 days. No significant adverse events were noted with the use of the device. The use of the micro-coring device Aime™ in a porcine model for skin fractional micro-excision and resurfacing was effective and safe. The comprehensive gradual healing process shown in this study with detailed histopathological images can also serve as a basis for future pre-clinical studies of fractional ablative devices. (DOI: 10.1293/tox.2022-0079; J Toxicol Pathol 2023; 36: 11–19)

Key words: resurfacing, micro-coring, plastic surgery, dermatology, rejuvenation

Introduction

In recent years, following the rise in life expectancy, there is an increased demand for skin rejuvenation procedures that can facilitate youthful appearance[1]. Since these are mostly cosmetic procedures, they should optimally be low-risk treatments, non-surgical and non-invasive, and result in minimal down-time[1]. One of the popular skin rejuvenation techniques is fractional resurfacing, in which microscopic columns of the skin are ablated, resulting in undamaged intervening skin that facilitate quick re-epithelialization. Damage to the dermis results in synthesis of collagen and formation of a new structural matrix, leading to increased skin tension, carrying the potential for several positive clinical outcomes[1–6].

Energy-based devices have been developed to achieve fractional resurfacing, by producing heat-induced ablation coagulation and necrosis of the dermis, leading to the formation of new cells[6, 7]. However, their use can result in side effects that include burns, hyper- or hypopigmentation, erosions, scarring, purpura and vascular necrosis[8, 9]. In addition, there is lack of data on the ability of fractional treatment lasers and radiofrequency devices to achieve skin tightening[10–12]. Another widely-used technique is microneedles, that present an excellent safety profile and quick recovery. However, since this technique does not result in tissue removal, significant skin tightening is difficult to achieve[12, 13].

The micro-coring technology (MCT) is a newly developed technology, designed to remove micro skin columns using hollow hypodermic needles, without scar formation and without thermal energy. Although MCT is a highly promising technique, there are very limited data, from two preclinical studies and one clinical trial, on its safety and effectiveness[12, 14, 15]. Therefore, we have performed a preclinical study using a swine model to assess the safety and efficacy of a new robotic, fractional micro-coring device, Aime™ (Venus Concept Inc., San Jose, CA, USA), designed for skin tissue excision and resurfacing.

Materials and Methods

Device

Aime™ is a robotic micro-coring device composed of six cores, with a diameter of 0.74 mm, which rotates (at 4,500 rpm) and cores the skin to a depth of 3 mm (Supplementary Fig. 1). A vacuum is applied via the hollowed syringes, to remove the cores from the skin, performing the excision.

Animal model and experimental design

The study comprised of four female domestic (sus scrofa domesticus) Large White pigs, approximately 4 months of age, each marked with 14 designated sites on their abdomen (up to 3 × 4 cm² per site). Twelve (12) sites were treated using Aime™, at 6 different time points: days 0, 14, 21, 25, 27 and 28. At each time point, 2 sites were treated (for a total of 12 treated sites, in each pig, by day 28) (Table 1 and Supplementary Fig. 2). The 10 sites treated prior to day 28 were sealed with Tegaderm™ (3M, Afula, Israel) film dressing, at full coverage, immediately following treatment. On day 0 alone, a single, 13th site was treated and left unsealed, serving as positive control. The 14th site was not treated and served as negative control.

On day 0, each designated treatment site was marked by squares on the animal's abdominal skin, drawn by a sterile, non-irritant, surgical skin marker (for one-off medical use), and by tattooing dashed lines surrounding each square. Each site was numbered. Coring was performed after the animals were anesthetized as follows: premedication was administered by intramuscular administration of a mixed solution of Ketamine (10 mg/kg) and Xylazine (2 mg/kg), followed by Isoflurane inhalation (1–3%, in oxygen 100%) at a flow rate of 3–4 L/min, administered by face mask. Following introduction of a venous catheter into the lateral ear vein, induction was achieved by intravenous (IV) injection of Diazepam (5–10 mg/animal). Intubation was performed by introduction of an appropriately sized, endotracheal

tube. Morphine was administered (0.5 mg/kg), by IM injection and anesthesia was maintained by isoflurane inhalation (1–3% in oxygen 100%) through the endotracheal tube. Supplemental Ketamine and Xylazine were administered IM during the procedures, per veterinarian discretion. Prior to coring, the abdominal area was clipped and disinfected by scrubbing with 4% (w/v) Chlorhexidine Gluconate (SEPTAL SCRUB®, TEVA MEDICAL LTD, Tel Aviv, Israel) and rinsing with ethanol 70%.

Treated sites (except for the positive control) and sites treated on day 28 were covered with Tegaderm™ film. The abdomen was wrapped with an elastic bandage, followed by wrapping with an elastic bandage mesh. On days 7, 21, 25, 27 and 28, the bandages were removed from all animals.

Animals were observed for a total duration of 28 days, and were provided with approximately 1.8 kg/ (pig × day) of commercial pig diet and were allowed free access to drinking water supplied by automated watering valves. Conditions were set to maintain temperature at 16–27°C and relative humidity at 30–70%. All animals were observed for morbidity, mortality, and injury at least twice daily throughout the study period. Furthermore, food and water consumption were qualitatively observed, at least once daily. Detailed clinical examinations of animals were carried out at least once weekly or more frequently when indicated by the response of the animals to the procedure. Determination of individual body weights was carried out during the acclimation period (pre-procedure), on procedure day or the day before and once weekly thereafter until study termination. Macroscopic evaluations of all sites were performed on study day 28, for acutely-treated sites and ones treated 1 day, 3, 7, 14, and 28 days prior, per animal, according to a semi-quantitative grading scale (Table 2).

Upon termination (day 28), animals were anesthetized as previously described. Two full thickness biopsies (a 10 mm punch and a 1 cm² square) were collected from each of the 14 sites (treatment and control) in 3 out of 4 treated animals (predetermined randomly). Punch biopsies were cut in the middle and both halves were embedded in a single paraffin block. Each square sample was cut in the middle and each section was embedded in paraffin. Blocks from all sites were cut at 3 levels (i.e., 1st level 0; 2nd level 200 μm; 3rd level 400 μm) of approximately 3–5 μm thickness each. All Sections were stained with hematoxylin and eosin (H&E).

Histopathological evaluations included the following parameters: size of skin excision—width and depth (morphometric evaluation); presence of focal hemorrhage and/

Table 1. Experimental Design

Total number of treated sites per animal	Total number of treatment sites per animal and study day						Observation period
	0	14	21	25	27	28	
n=13*	3	2	2	2	2	2	28 days

* In addition, one untreated site (negative control) was sampled on day 28.

Table 2. Macroscopic Evaluation of Local Reactions

Score	Erythema	Edema	Scabs/Crust
0	No erythema	No edema	None
1	Very slight erythema (barely perceptible)	Very slight edema (barely perceptible)	Light
2	Well defined erythema	Well defined edema	Moderate
3	Moderate to severe erythema	Moderate edema (raised ~1 mm)	Heavy
4	Severe erythema (beet redness)	Severe edema (raised more than 1 mm)	-

or blood clot (semiquantitative evaluation); presence of focal inflammation (semiquantitative evaluation); epidermal migration/regeneration/re-epithelization (semiquantitative evaluation); presence of focal epidermal hyperplasia (semiquantitative evaluation), presence of focal epidermal/dermal crust (semiquantitative evaluation); presence of foci of fibroblastic and/or collagen synthesis (semiquantitative evaluation); presence of healed resurfaced area (yes/no evaluation). Morphometric evaluation was performed using the Augmentiqs system https://www.augmentiqs.com/)[16]. All parameters were graded based on a 5-grade (0–4) scale[17]: Grade 0 - No change; Grade 1 - minimal change; Grade 2 - mild change; Grade 3 - moderate change; Grade 4 - severe change.

This study was performed at The Institute of Animal Research (Kibbutz Lahav, Israel), following approval from the National Council of Animal Experimentation (Number NPC-La-IL-2112-175-4), and in compliance with Good Laboratory Practice (GLP)-guidelines.

Statistical evaluations

Calculations and statistical evaluations were performed with Excel® (Microsoft Ltd., Redmond, WA, USA). Statistical significance was defined as $p < 0.05$, found in a comparison of means, applied with non-parametric tests (Mann–Whitney U test [with Kruskal–Wallis test applied for multiple comparisons]).

Results

Clinical evaluation

No mortality had occurred in any of the animals throughout the entire observation period, and there were no abnormal clinical signs that required treatment. All animals gained weight normally during the observation period.

Macroscopic evaluations of treated sites

Erythema scores for all sites ranged from 3 (moderate) to 4 (severe) on treatment day and decreased gradually starting from two days after the treatment. By 28 days following treatment, no erythema was observed (Table 3 and Supplementary Figs. 3–6). Edema scores for all sites ranged between 1 (very slight, barely perceptible) to 2 (well defined edema) on treatment day. The scores either increased by one point (with no score above 2 noted) or remained at the same value, following 1 day, and gradually decreased following 3 days. By 28 days following treatment, no edema was observed (Table 4 and Supplementary Figs. 3–6). No scab or crust were observed for any examined time point following treatment.

Microscopic evaluations of treated sites

The histopathologic evaluation of the treated sites showed a clear time-related progressive process of healing (Fig. 1A–P). The healing process was characterized by progressive re-coverage of the tissue excision-tested sites with complete, well differentiated, newly formed epidermis, associated with efficient elimination of the underlying, well circumscribed hollow spaces and the necrotic dermis, and its eventual replacement by maturing fibroplasia (Tables 5–10). In some sites, complete healing was evident already following 7 days post treatment.

For the earlier stages of evaluation (days 0, 1 and 3 following treatment), the well circumscribed, rectangular-like necrotic areas progressively reduced in size, and were associated (from day 1) with relatively minor acute inflammatory reaction, which subsided completely in the later examined time points (Table 11). The developing fibroplasia replaced and filled the previously necrotic sites. The overlying newly formed epidermis demonstrated only minimal focal increased thickness, reflecting hyperplasia, which returned to standard thickness at the more advanced stages (from day 7) of healing (Table 12). No side effects, such as burns, hyper- or hypopigmentation, erosions, scarring, purpura or vascular necrosis were noted in any of the examined samples.

Table 3. Erythema Scores

Days post activation	28	14	7	3	1	0
Animal 1	0	1	1	2	3	3
	0	1	1	2	3	3
Animal 2	0	0	2	2	3	3
	0	1	1	2	3	4
Animal 3	0	1	2	2	2	3
	0	1	1	2	3	3
Animal 4	0	0	2	2	2	3
	0	1	2	2	2	3
p-value compared to day 28		0.01	0.00	0.00	0.00	0.00
p-value compared to day 14			0.04	0.00	0.00	0.00
p-value compared to day 7				0.10	0.00	0.00
p-value compared to day 3					0.04	0.00
p-value compared to day 1						0.14

Table 4. Edema Scores

Days post activation	28	14	7	3	1	0
Animal 1	0	1	1	2	2	2
	0	2	1	2	2	1
Animal 2	0	0	1	1	2	1
	0	1	1	2	2	1
Animal 3	0	1	2	2	1	1
	0	1	1	1	2	1
Animal 4	0	0	1	2	2	1
	0	1	1	2	2	1
p-value compared to day 28		0.01	0.00	0.00	0.00	0.00
p-value compared to day 14			0.49	0.02	0.01	0.49
p-value compared to day 7				0.04	0.01	0.96
p-value compared to day 3					0.71	0.04
p-value compare to day 1						0.01
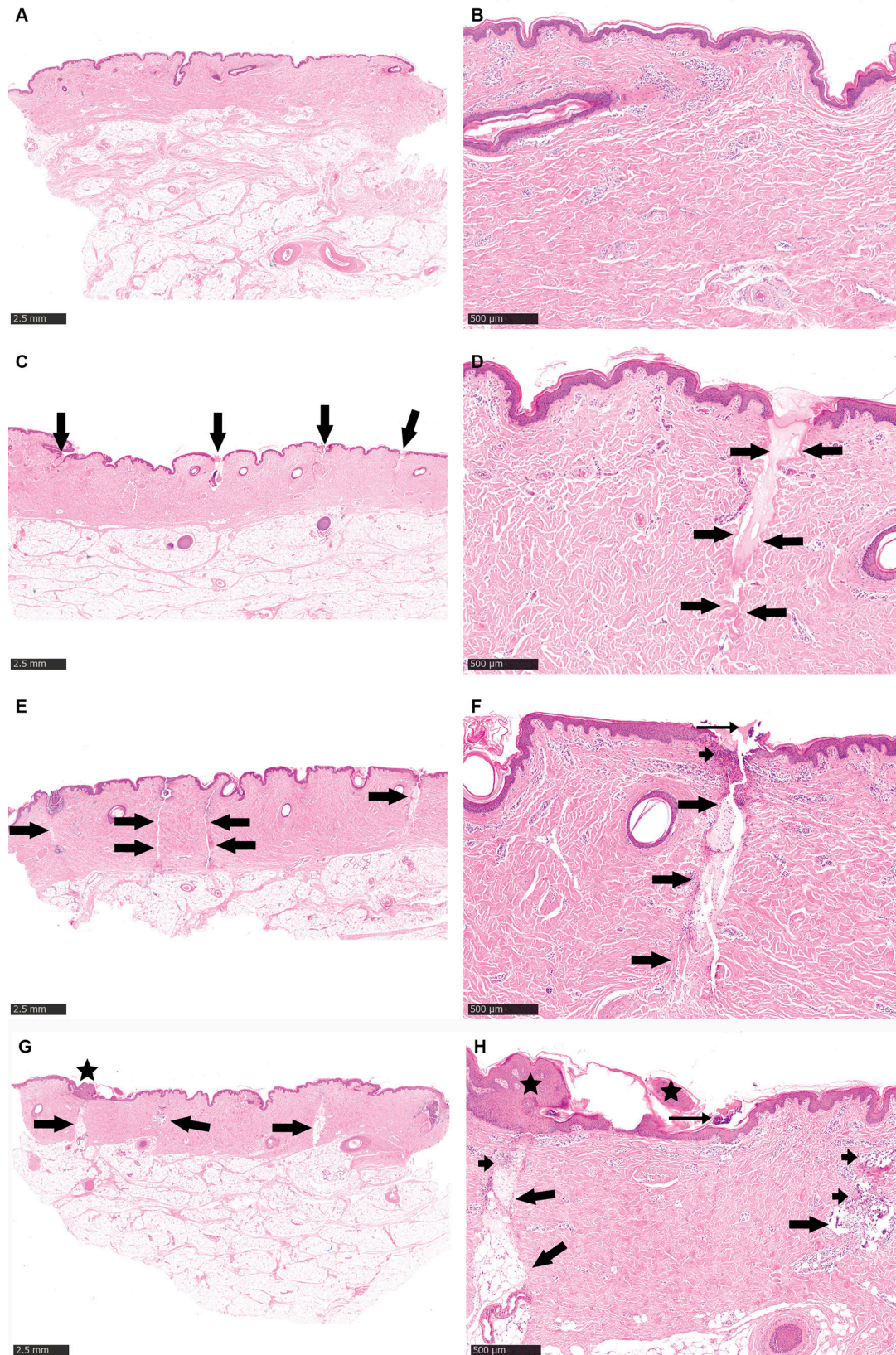
Fig. 1. A and B. Negative control site, no abnormality seen at low (A) or high (B) magnifications. **C and D.** Day 0, immediately after treatment. Note multiple epidermal and dermal hollow excision site (arrows). Low (C) and high (D) magnifications. **E and F.** Day 1 after treatment. Image shows multiple epidermal and dermal hollow excision sites (thick long arrows), epidermal crust formation (thin long arrow) and epidermal and dermal inflammation (thick short arrow). Low (E) and high (F) magnifications. **G and H.** Day 3 after treatment. Image shows multiple epidermal and dermal hollow excision sites (thick long arrows), epidermal crust formation (thin long arrow), epidermal hyperplasia (asterisk) and epidermal and dermal inflammation (thick short arrow). Low (G) and high (H) magnifications.
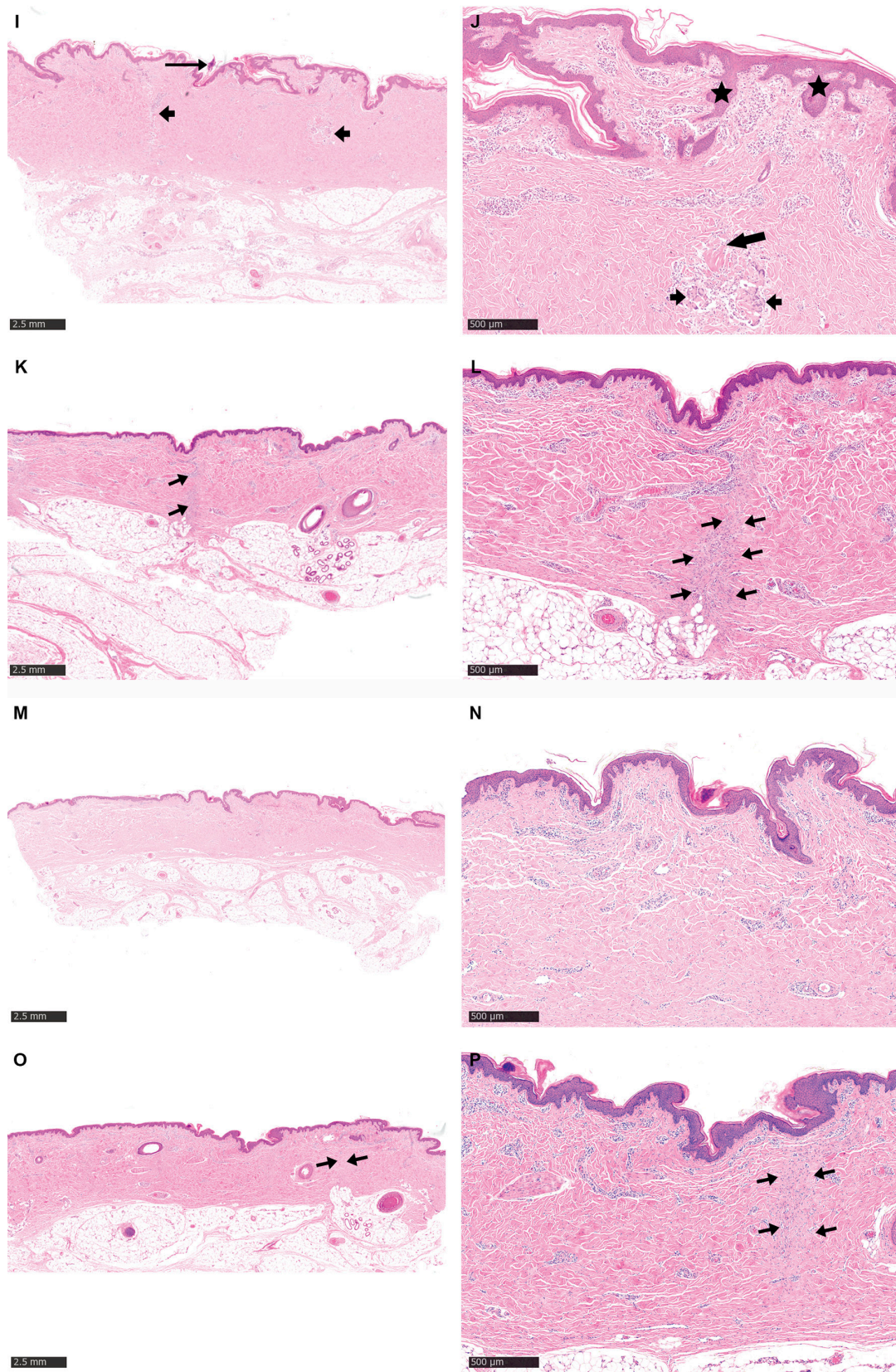
Fig. 1. **I and J.** Day 7 after treatment. Image shows dermal hollow excision sites (thick long arrow), epidermal crust formation (thin long arrow), epidermal hyperplasia (asterisk) and epidermal and dermal inflammation (thick short arrow). Low (I) and high (J) magnifications. **K and L.** Day 14 after treatment. Image shows dermal fibrosis filling the sites of the excision (thick short arrows). Low (K) and high (L) magnifications. **M and N**. Positive control site, no abnormality seen. Low (M) and high (N) magnifications. **O and P.** Day 28 after treatment. Image shows dermal fibrosis filling the sites of the excision (thick short arrows). Low (O) and high (P) magnifications.

Table 5. Width of the Excised Tissue (Data in Millimeters)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	0	0	0	0	7.3	9.5	0	0	0	0	7.4	7.1
	0	0	0	0	0	10.9	0	0	0	0	5.9	6.2
Animal 3	0	0	0	0	8.4	9.7	0	0	0	0	8.9	7.2
	0	0	0	0	8.6	14.3	0	0	0	0	6.7	7.2
Animal 4	0	0	0	0	11.1	4.2	0	0	0	0	0	2.9
	0	0	0	0	10.9	13.4	0	0	0	0	6.7	4
p-value compared to day 28		0.93	0.93	0.93	0.02	0.00			0.93	0.93	0.02	0.00
p-value compared to day 14			0.93	0.93	0.02	0.00				0.93	0.02	0.00
p-value compared to day 7				0.93	0.02	0.00				0.93	0.02	0.00
p-value compared to day 3					0.02	0.00					0.02	0.00
p-value compared to day 1						0.26						0.81

Table 6. Depth of the Excised Tissue (Data in Millimeters)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	0	0	0	0	1.4	1.2	0	0	0	0	0.8	0.7
	0	0	0	0	0	1.3	0	0	0	0	0.9	0.7
Animal 3	0	0	0	0	0.4	1.2	0	0	0	0	0.4	0.9
	0	0	0	0	0.5	2.6	0	0	0	0	0.5	0.8
Animal 4	0	0	0	0	1.8	0.9	0	0	0	0	0	0.4
	0	0	0	0	2.7	1.3	0	0	0	0	1.3	1
p-value compared to day 28		0.93	0.93	0.93	0.02	0.00			0.93	0.93	0.02	0.00
p-value compared to day 14			0.93	0.93	0.02	0.00				0.93	0.02	0.00
p-value compared to day 7				0.93	0.02	0.00				0.93	0.02	0.00
p-value compared to day 3					0.02	0.00					0.02	0.00
p-value compared to day 1						0.81						0.74

Table 7. Hemorrhage and/or Blood Clots (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	0	0	0	1	1	2	0	0	0	0	2	2
	0	0	0	1	2	2	0	0	0	1	2	2
Animal 3	0	0	0	0	2	2	0	0	0	0	2	2
	0	0	0	0	2	2	0	0	0	0	2	2
Animal 4	0	0	1	0	1	1	0	0	1	2	1	1
	0	0	0	0	2	2	0	0	1	0	2	1
p-value compared to day 28		0.93	0.68	0.37	0.00	0.00			0.93	0.37	0.37	0.00	0.00
p-value compared to day 14			0.68	0.37	0.00	0.00				0.37	0.37	0.00	0.00
p-value compared to day 7				0.68	0.00	0.00				0.93	0.00	0.01
p-value compared to day 3					0.01	0.00					0.03	0.04
p-value compared to day 1						0.68						0.68

Discussion

Here we present a detailed histological and clinical evaluation of the efficacy and safety of a novel micro-coring device developed for fractional skin excision and resurfacing, in domestic pigs model. This is one of few studies performed in pigs for the evaluation of a micro-coring device, and the first to show detailed histological images of the complete gradual healing process expected with this device.

To the best of our knowledge, only two pre-clinical studies were previously performed with a micro-coring device, both performed in pigs. The first followed one animal for 3 months, and similar to this study, initial erythema was seen in all treated sites[14]. However, as was also shown in this study, the erythema quickly subsided—a fact that is in sharp contrast to the redness seen in patients treated with ablative

Table 8. Epidermal/dermal Crust (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	1	1	1	2	0	0	1	2	2	1	2	0
	1	1	2	2	0	0	0	1	2	2	2	0
Animal 3	0	0	1	1	1	0	1	1	0	1	1	0
	0	0	1	1	0	0	0	1	0	1	1	0
Animal 4	0	1	1	1	1	0	0	0	1	1	1	0
	0	0	1	1	0	0	0	0	0	1	1	0
p-value compared to day 28		0.68	0.04	0.03	0.93	0.37		0.29	0.47	0.04	0.03	0.37
p-value compared to day 14			0.10	0.06	0.68	0.17			1	0.47	0.29	0.06
p-value compared to day 7				0.68	0.04	0.00				0.52	0.37	0.17
p-value compared to day 3					0.03	0.00					0.68	0.00
p-value compared to day 1						0.37						0.00

Table 9. Dermal Necrosis (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	0	0	0	2	1	3	0	0	0	0	2	3
	0	0	1	2	2	3	0	0	0	2	2	3
Animal 3	0	0	1	2	2	2	0	0	0	2	2	2
	0	0	1	2	2	2	0	0	1	2	2	2
Animal 4	0	0	1	2	2	2	0	0	1	1	2	2
	0	0	0	2	2	2	0	0	1	2	2	2
p-value compared to day 28		0.93	0.06	0.00	0.00	0.00		0.93	0.17	0.02	0.00	0.00
p-value compared to day 14			0.06	0.00	0.00	0.00			0.17	0.02	0.00	0.00
p-value compared to day 7				0.00	0.01	0.00				0.06	0.00	0.00
p-value compared to day 3					0.68	0.37					0.37	0.12
p-value compared to day 1						0.22						0.37

Table 10. Fibroplasia and/or Collagen Synthesis (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	0	3	0	0	0	0	0	3	3	0	0	0
	0	3	3	0	0	0	0	3	3	0	0	0
Animal 3	0	3	3	0	0	0	0	3	3	0	0	0
	0	3	3	0	0	0	0	3	3	0	0	0
Animal 4	3	3	3	0	0	0	3	3	3	0	0	0
	3	3	3	0	0	0	3	3	3	0	0	0
p-value compared to day 28		0.06	0.17	0.37	0.37	0.37		0.06	0.06	0.37	0.37	0.37
p-value compared to day 14			0.68	0.00	0.00	0.00			0.93	0.00	0.00	0.00
p-value compared to day 7				0.02	0.02	0.02				0.00	0.00	0.00
p-value compared to day 3					0.93	0.93					0.93	0.93
p-value compared to day 1						0.93						0.93

lasers, which result in erythema that can last for 3 months or even more after treatment[18]. In an additional study in pigs, less than a third of coring sites had erythema at day 7 after treatment, similar to this study where by 28 days there was no erythema in all treated sites[15]. The excised skin in this study did not have any scar, and we have also seen—macroscopically and histologically—complete healing of the epidermis, with no signs of scarring, as early as 7 days after

treatment. No inclusion cysts were seen in this study.

While this study included observation of the treated sites for a relatively short period of time (28 days), which might not be enough to encompass the full collagenosis process in the dermis, we could see that collagen synthesis and fibroplasia were evident at 7 days after treatment and continued throughout the healing process. This process is expected to eventually lead to improvement in the clinical appearance

Table 11. Inflammation Scores (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	1	0	1	1	2	0	1	0	1	1	2	0
	0	0	1	2	2	0	0	0	1	2	2	0
Animal 3	0	1	1	2	1	0	0	1	1	2	1	0
	0	1	1	2	1	0	0	1	1	2	1	0
Animal 4	0	1	1	2	2	0	0	1	1	2	2	0
	0	0	1	2	2	0	0	0	1	2	2	0
p-value compared to day 28		0.37	0.02	0.00	0.00	0.68		0.37	0.02	0.00	0.00	0.93
p-value compared to day 14			0.17	0.01	0.02	0.17			0.17	0.02	0.01	0.37
p-value compared to day 7				0.02	0.06	0.00				0.10	0.04	0.02
p-value compared to day 3					0.68	0.00					0.68	0.00
p-value compared to day 1						0.00						0.00

Table 12. Epidermal Migration/Regeneration/Re-epithelization (Semiquantitative Data)

Days post activation	Square sample						Punch sample					
	28	14	7	3	1	0	28	14	7	3	1	0
Animal 1	4	4	4	4	3	0	4	4	4	4	3	0
	4	4	4	4	4	0	4	4	4	4	3	0
Animal 3	4	4	4	4	3	0	4	4	4	3	3	0
	4	4	4	4	3	0	4	4	4	4	3	0
Animal 4	4	4	4	4	3	0	4	4	4	4	3	0
	4	4	4	4	3	0	4	4	4	3	3	0
p-value compared to day 28		0.93	0.93	0.93	0.02	0.00		0.93	0.93	0.37	0.00	0.00
p-value compared to day 14			0.93	0.93	0.02	0.00			0.93	0.37	0.00	0.00
p-value compared to day 7				0.93	0.02	0.00				0.37	0.00	0.00
p-value compared to day 3					0.02	0.00					0.06	0.00
p-value compared to day 1						0.00						0.00

of sun damaged skin and to skin rejuvenation[19–21]. Indeed, skin sites of a pig that were treated with a micro-coring device and followed for 3 months showed almost 90% increase in collagen content[14].

We have specifically evaluated the inflammatory response in the treated sites, since the inflammatory response in skin treated with lasers can demonstrate significant inflammatory response, which can persist for several weeks[21, 22]. In the current study, the inflammatory response as observed by histological examination, showed only mild degree of inflammation, with quick resolution, similar to previous findings[14].

Although still very preliminary, three clinical trials were performed in humans with MCT. The patients were followed for 90 days, and the results showed that non-scarring healing can also be seen in humans, similar to the observed effects in the porcine model. Side effects were generally mild, and like the ones seen in pigs, were quick to resolve[12]. It is expected that with further refinement of the technique of using these devices, efficacy, and safety of MCT in humans, can be further improved. Additional experimental, pre-clinical studies with comprehensive histopathological examinations, can enhance refinement of the technique.

The use of the novel micro-coring device, Aime™, in a porcine model of skin fractional micro-coring and resurfacing, resulted in a progressive process of healing, with replacement of the excised skin with maturing fibroplasia. In many of the sites, complete healing was observed as early as 7 days post-treatment. No significant adverse events were noted with the use of the device. The comprehensive gradual healing process shown in this study, with detailed histopathological images, can serve as a basis also for future pre-clinical studies of fractional ablative devices.

Disclosure of Potential Conflicts of Interest: None.

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