Clinical Proof-of-Concept Study on Split-Thickness Skin Grafting and Excision of Necrosis

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Abstract

Three (3) proof-of-concept, porcine studies were used to analyze safety and efficacy of a new dermatome for the tangential excision of necrosis in a deep partial thickness burn model and the harvesting of split-thickness skin grafts. The new device, Amalgatome® SD, is a pneumatic dermatome which uses a circular excision blade that rotates at high speed and has a dissection range of 180 degrees. The Amalgatome SD was designed to increase ease of use and to obtain a higher degree of consistency of the excised tissues. Standard dermatomes were used as the control device in the study: excisions and graft harvesting were performed in a randomized way.

In two of the three studies, the new test device was used to harvest skin grafts: donor sites and grafts were analyzed for viability, healing rate and scar outcomes. The new device was similar to control device with regards to viability of collected tissue, speed of healing and donor site biomechanics. The donor sites in the control device group showed significantly more hyperpigmented than in the test device group.

In one of the graft harvesting studies as well as in the Debridement I/excision study, the thickness of the excised tissues was measured using a calibrated microscope: uniformity of the thickness of the harvested tissues (STSGs as well as necrotic tissues) was better for the test device than for the control devices.

With regard to ease of use, the test device performed better than the control on several aspects; including maneuverability, control of the consistency of the relationship between the depth setting and the actual graft thickness, device assembly, overall ease of use, the depth of the debridement as intended, consistency of the debridement thickness, device accuracy, and size. Subjectively, the amount of blood loss during excision of necrosis was less for the test device as well.

The studies showed that the test device, when compared to the control devices, was equal on safety. On efficacy, consistency of the excised tissues was superior for the test device which may result in better grafts and better outcomes. Several aspects related to the ease of use, particularly maneuverability, were superior as well.

Introduction

Dermatomes are primarily used for removal of necrosis and the harvesting of a split-thickness skin graft (STSG). For tangential excision of necrosis, the most commonly used devices are the Humby knife[1] and Goulian Weck dermatome,[2] both hand-driven devices that have not changed substantially since their invention in the 1930s. Both devices can also be used to harvest STSG, although, particularly for larger grafts, mechanical (air-driven or electric) dermatomes are more commonly used. With the latter, the thickness of the excised tissue is better controlled and it is possible to take longer and more consistent grafts.[3]

The "typical" dermatome, whether mechanical or hand-driven, uses a straight blade in an oscillating fashion. The excisional direction is perpendicular to the oscillation, away from the dermatome operator. The thickness of the excision is set by using a guard plate for hand-driven dermatomes while mechanical dermatomes usually have a depth adjustment dial set on the side.

Excision of the proper amount of necrosis without sacrificing viable layers of tissue underneath has been proven difficult,[4] even with the modern dermatomes. "Shelving" can occur because of variances in the depth of excisions and the "angle of attack", the angle between the knife and the skin, also influences the actual thickness of excision.[5] Adjusting the thickness of excision during operation is very difficult because of the location of the depth-adjustment dial on the side of the device while, when a hand-driven dermatome is used, the surgical procedure must be interrupted to install a different depth gauge.

Powered dermatomes are pushed away from the surgeon while hand-driven dermatomes are drawn toward the operator. Hand-driven dermatomes have a steep learning curve and limited fidelity. Powered dermatomes also have limited fidelity and have intrinsic difficulties engaging tissues: they are rarely used for (tangential) excision.

Alternatives to debridement or tangential excision of necrosis with a dermatome include non-contact, low-frequency ultrasound and hydrosurgery[6, 7] as well as a specific type of bromelain enzyme.[8, 9]

These alternatives have their own peculiarities and a learning curve[10-12] while pain is associated with the bromelain procedure.[13] Other enzymes are significantly less successful, at least in burn care, because the inconsistency and unreliability of their results.[10-12, 14] Maggot therapy is safe and very effective but relatively slow versus surgical excision[15] and carries a strong psychological burden.[16, 17] Excision and debridement with different types of lasers, tested in burn care, was reasonably successful but never have become common therapies.[18, 19]

To overcome challenges associated with the ability to observe the harvest site during operation and make real-time changes in harvest depth, an easy-to-use dermatome was developed.

FIGURE I

AMALGATOME® SD, 2-INCH AND 4-INCH VERSION. NOTE THE DEPTH GAUGE ON TOP OF THE DEVICE AND THE "WINDOWS" THROUGH WHICH TISSUE TO BE EXCISED CAN BE VIEWED.

The Amalgatome® SD♦ (Figure I) is a new air-powered dermatome that utilizes a circular excision blade that rotates at high speed and has a dissection range of 180 degrees. The handle has a 15% angle versus the blade, minimizing the need for the operator to put pressure on the dermatome. This, in turn, lowers the chance for inconsistencies and shelving in the thickness of the graft taken. The depth limiting plate on the instrument is designed to flatten the skin as it approaches the cutting edge. The dermatome is also pulled towards the operator, instead of being pushed away, and allows for better control of the instrument's movement. As the depth gauge is on the top of the device, the depth setting (0.005-.040", 0.127 1.016mm) can be changed without having to stop the surgical procedure. The dermatome exists in a 4-inch and 2-inch head assembly; they use different plates/blade guards for width adjustment.

The instrument has been designed to overcome the major drawbacks of conventional dermatomes, primarily aiming at improving the ability to tangentially excise tissue, maneuverability and the consistency of thickness of excised tissue. Together, this should result in potentially greater graft yield since they can be taken from areas that are difficult to use with the conventional dermatomes, including bony prominences and contoured areas. The entire design also aims at increasing ease-of-use aspects, such as simplicity in assembling and disassembling.

To evaluate the functionality of the Amalgatome SD (test device), three porcine, proof-of-concept studies were performed, comparing the test device to three different types of air-driven dermatomes (control devices). In one study (Debridement I), uniformity of excised necrotic tissue was measured while the second study (STSG I) focused on different aspects of STSG harvesting, both with regard to the donor site as well as the grafts obtained. A third study (STSG II) addressed different aspects of STSG harvesting and primarily looked at different facets of the donor site. The primary objective of all studies was to characterize the performance and safety of the test device in the different indications, when compared to conventional dermatomes (control devices). Excised tissues (burn necrosis and STSG) were tested on uniformity with regard to thickness, and viability was evaluated for STSGs. Donor site evaluation included biomechanical properties, speed of re-epithelialization, rate of contraction, the level of post-operative erythema and pigmentation. Secondary objectives in study Debridement I and STSG I also included aspects of overall ease of use and maneuverability.

♦ Exsurco Medical Inc., Wakeman, OH, USA

Methods

GENERAL PROCEDURES

All studies were conducted in accordance with FDA Regulations on Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies CFR Title 21 Part 58 and used institution-approved protocols. Studies Debridement I and STSG I were performed by NAMSA.♦ Study STSG II was performed following a protocol approved by the Institutional Animal Care and Use Committee at The Ohio State University. Both are AAALAC International accredited institutions.

Husbandry and basic operation protocols were similar for all studies, although each facility used its own approved standard operating procedures. All studies were prospective, non-blinded, and randomized in character.

For Debridement I and STSG I, four female Yorkshire Cross swine were used. The animals were 3-4 months old and weighed approximately 60 kg at the date of the initial procedure. For study STSG II, similarly aged, female red Duroc pigs were used. Animals were verified to be in good health through a physical exam performed by testing facility veterinary care staff at the time of arrival and within two days prior to the study procedure. Feed and water was provided per testing facility SOPs. Diet was a commercially available feed from a testing facility approved supplier.

For all studies, on the day of the procedures, animals were sedated, intubated and prepped for procedures with an antiseptic scrub. Wounds were dressed post-operatively with a neutral, non-adherent, and a fixation dressing. Post-operative pain was properly addressed (e.g. with Novaplus Fentanyl patches¥). Animals were recovered from anesthesia and returned to general housing. During the in-life portion of the study, animals were observed daily for overall health by animal care staff. For Debridement I and STSG I, each wound and the surrounding tissues were observed, scored by a test facility veterinarian, and photographed daily.

For studies Debridement I and STSG I, 28 (±2) days after skin harvest and necrosis excision procedures, animals were sedated and anesthetized and humanely euthanized. A general necropsy was performed. Wounds were visually evaluated, measured, and described and subsequently excised and preserved in 10% Neutral Buffered Formalin for histological evaluation. Histological thickness measurements were taken to the nearest 1000th of an inch with a calibrated microscope. Pre-and post-operative bloodwork included hematology (CBC w/ diff) and standard serum profile, including tests for liver and renal functions.

For study STSG II the time of humane euthanasia was 30 days post-harvesting procedure.

SPLIT SKIN GRAFT STUDY PROCEDURES, STUDY STSG I

In this study, six (6) wounds (3 on the left, 3 on the right of the spine) were created in a randomized fashion, using either the test or control device. A total of four pigs was used, thus creating 24 lesions. Wounds were located at a minimum of 2.5 cm from the midline spine and spaced evenly down the

♦ NAMSA, Brooklyn Park, Minnesota, MN, USA
¥ Watson Pharmaceuticals, INC, Parsippany, NJ

extent of the dorsal crest. STSGs were harvested with the 4-inch head test device (rotating blade), the Humeca®♠ D80STS battery powered dermatome and the Integra®♥ Padgett® Electric Powered Dermatome (controls devices, both with oscillating blades).

The donor sites were 7.0-9.5 cm (length) x 5.0-10.0 cm (width) x 0.018-0.025 cm (depth).

Each donor site was observed and scored on the levels of edema and erythema (range: absent to severe), the presence and percentage of granulation tissue (range: absent to over granulation) and the level of re-epithelialization (range: absent to complete re-epithelialization) by a qualified veterinarian. Cover dressings were changed daily and remained in place for a duration as deemed necessary by a testing facility veterinarian. Animals were placed in jackets to prevent disruption to donor sites. Antibiotic and analgesic therapy were administered if and when necessary. At the end of the study, at days 28 (± 2) animals were euthanized and tissues harvested as per the procedures described above. At this point, biopsies were taken for histological analysis.

DEBRIDEMENT PROCEDURES, STUDY DEBRIDEMENT I

In this study 24 burns were created in a randomized fashion and spaced similarly to those in study STSG I. Six mid to deep dermal burns, approximately 4 cm in diameter, were created using a modified validated model[20] with an aluminum rod, heated by submersion in boiling water for approximately 15 to 20 minutes. The rod was then applied without pressure to the dorsum of the animal for 20-40 seconds. The burns were dressed with a non-adherent, absorbing bandage. Three days after the burns were created, when the lesions were clinically determined to have an appropriate amount of blistering and necrotic tissue to undergo debridement, the animals were sedated, anesthetized and prepared for the procedures. The 2-inch version of the test device was used for tangential excision and compared to the (manual) Goulian Weck Skin Graft Knife, commonly referred to as Weck Knife, as control.√ The burn wounds were debrided using both the test and control device in accordance with the instructions for use for the different dermatomes and with fixed settings. The excised specimens of necrotic tissue were prepared for histological evaluation.

Post-operative procedures were, essentially, similar to those in study STSG 1 as was the analysis and scoring of the wounds. 28 (±2) days after the debridement procedures, animals were sedated and humanely euthanized with an IV overdose of a barbiturate-based euthanasia solution. Histological specimens were taken, and a limited necropsy was performed.

SPLIT SKIN GRAFT STUDY PROCEDURES, STUDY STSG II

In study STSG II, the test device was compared to a Zimmer air dermatome.♥ Wounding was done in a randomized fashion and by a single surgeon. The wounding protocol was separated in two different segments.

For an analysis on uniformity of thickness, 6 mm punch biopsies at 3 cm intervals were collected from each graft harvested at different dermatome thickness settings (0.012-0.018″). Biopsies were

♠ HUMECA, Borne, the Netherlands
♥ Integra LifeSciences Corporation, Plainsboro, NJ, USA

√ Multiple manufacturers, (may be listed under Teleflex Medical)
♥ Zimmer Biomet, Warsaw, IN USA

placed between two glass slides and measured using digital calipers. To evaluate the total amount of skin harvested, as well as the amount of usable skin (for this measurement, areas that were too thin or irregular were excluded), each piece of skin was photographed, digitized and total area measured using computerized planimetry.

Graft viability was measured using an MTT assay, as previously described,[21] with punch biopsies, taken approximately 3 cm apart down the length of the graft randomizing edge versus center collection points. Six sites from each graft (n = 6 per device) were assessed with average absorbance + standard error of the mean plotted. Higher absorbance indicates a higher level of cellular metabolism which, in turn, indicates greater viability.

In the second part of STSG II, re-epithelialization and donor site contraction, color and biomechanics were assessed on six different animals. A 2-inch-wide by 10-inch-long split-thickness skin graft was harvested in either side of the dorsum with collection device site randomized. Trans-epidermal water loss (TEWL, Tewameter♦ TM 300) measurements were collected at 3, 7, 14 and 29 days post-harvesting with three individual measurements per donor site collected at each time point and presented as average TEWL + standard error of the mean. Photographs and tracings of each donor site were collected at the same time points with tracings scanned (Brother MFC-8710DW♠) and total donor site area assessed using ImageJ (ImageJ software♥). Donor site contraction was calculated by dividing the measured area at a given time point (Af) by the size of the initial area (Ai) multiplied by 100. Average % original area + standard error of the mean was plotted for each group at each time point.

At the final time point (day 29), donor site pigmentation and erythema were assessed using a Mexameter.♦ The device exposes the skin to light at three different wavelengths (568 nm, 660 nm, and 870 nm) and calculated the quantity of light absorbed by the skin at each wavelength. The redness of the skin (erythema) and pigmentation of the skin was quantified at three different points along each donor site (n = 6 donor sites per device) and normalized to erythema and pigmentation of the surrounding skin (as measured for each pig). Results were plotted individually as normalized color for each pig and as an average deviation for normal for all pigs.

Biomechanics of the donor site at day 29 post-harvesting were measured using a BTC-2000♣ and a torsional ballistometer.▼ The BTC-2000 is a hand-held device that applies suction to the skin and measures the deformation of the skin in response to the suction. Skin stiffness, elasticity, and laxity (pliability) were calculated from the time-displacement curves.

♦ COURAGE+KHAZAKA electronics GmbH, Cologne - Germany
♠ Brother International, Bridgewater, NJ, USA
♥ NIH, Bethesda, MD, USA
♣ SRLI technologies, Franklin TN, USA
▼ Dia-Stron, Clarksburg, NJ, USA

Statistical Analyses

All data at study STSG II were compared using a Student's t-test (Sigma Stat v.12) with $p < 0.05$ considered statistically significant.

Results

The primary objective of these studies was to compare the test device with conventional devices on performance and safety in the harvesting of STSGs and excision of necrosis, while secondary objectives included aspects of healing as well as ease of use. With regard to safety, none of the animals in any of the studies developed any adverse experiences and all remained healthy throughout the study while all procedures were successfully completed. There were no significant changes in any of the values in the blood tests on any of the animals during the study.

SPLIT SKIN GRAFT STUDY, STSG I

Post-operative observation showed low and comparable levels of erythema and edema amongst the different wounds, while the development of granulation tissue was similar with regard to percentage of the wound surface and speed of development. Histologically, all lesions showed similar amounts of (minimal) fibrosis in the dermis and signs of cellular infiltration and inflammation also were similar. All wounds showed a similar overall healing profile over time and were completely re-epithelialized by the end of the study (post-operative day 28).

Graft thickness, measured with a calibrated microscope, was more consistent (smaller variance) for those taken with the test device than the control

TABLE I

1a. STUDY STSG I: GRAFT TISSUE, THICKNESS (INCHES)

	Test Dermatome	Control Dermatome
Avg	0.0174	0.0174
Min	0.0080	0.0050
Max	0.0320	0.0350
SD	0.0059	0.0081

1b. DEBRIDEMENT STUDY, THICKNESS OF EXCISED NECROSIS (INCHES)

	Test Dermatome	Control Dermatome
Avg	0.021	0.058
Min	0.008	0.020
Max	0.033	0.089
SD	0.007	0.015

1c. DEBRIDEMENT STUDY, DIFFERENCE BETWEEN DERMATOME SETTING AND MEASURED THICKNESS OF EXCISED TISSUE (INCHES)

	Test Dermatome	Control Dermatome
Avg	0.003	0.049
Min	-0.002	-0.063
Max	0.009	-0.018
SD	0.003	0.014

devices (Table Ia). The test device also obtained better scores than control on the consistency of the relationship between the depth setting and the actual graft thickness, as well as on overall device size and maneuverability. Ratings on ease of sterilization, assembly, and disassembly, as well as with regard to "usage as intended" and "use within intended margins" were similar among the test and control device.

DEBRIDEMENT STUDY, DEBRIDEMENT I

The objective of this study was to compare the performance and safety of two types of dermatomes when used for excision of dermal necrosis in deep partial thickness burns. Debridement procedures were successful for all wounds.

Erythema and edema scores were similar between the test- and control devices-created excisional wounds, and relatively high immediately after debridement. They gradually decreased when time progressed. No differences were observed with regard to the post-excision development of granulation tissue and re-epithelialization. Control sites were noted to have discharge (either serous or sero-sanguinous) throughout the study more frequently than test sites. The average wound size (including contraction) at study end was approximately similar for the test and control device (3.20 cm2 and 3.182 cm, respectively) with normal and complete healing.

Thickness measurements with a calibrated microscope of the excised necrotic tissues showed a narrower range of thickness (0.021 inch. on average, min: 0.008, max: 0.033, SD 0.007) than for the control (0.058 inch. on average, min: 0.020, max: 0.089, SD: 0.015) (Table Ib). For the test device, a higher level of accuracy and repeatability with regard to the dermatome setting as well as for the actual thickness of the excised tissue was demonstrated (Table Ic).

The test device subjectively scored better on device assembly, overall ease of use, the depth of the debridement as intended, consistency of the debridement thickness, the amount of blood loss (less loss of blood provided a better score), device accuracy, and the device size. Test and control device received equal scores on other aspects of use, such as "instructions that were easy to follow", usage of the devices as intended, ability to use the devices within the intended margin, maneuverability, and ease of device disassembly.

SPLIT SKIN GRAFT STUDY, STSG II

For each device, there was no difference in the usable quantity of tissue (i.e. no areas of graft too thin for usage). Viability, as measured by MTT,[21] was not significantly different between the test and control devices for all pigs except for number 6 (Figure IIa) with no detectable difference when all data were as collated (Figure IIb; p = 0.875).

Trans-epidermal water loss (TEWL), which directly quantifies the re-establishment of epidermal barrier function, decreased as a function of time post-harvesting in both groups. At post-operative day 14, the donor site in the test group had significantly lower TEWL (Figure III); no significant difference was detected, however, at any other time point and donor sites from both groups reached baseline by day 29. Donor site contraction was not significantly different between the control and the test device (p >0.05) (Figure IV).

FIGURE IIa
GRAFT VIABILITY, AVERAGES FOR TEST AND CONTROL DEVICE PER PIG

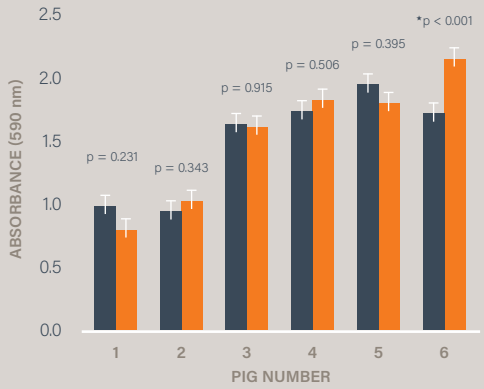


FIGURE IIb
GRAFT VIABILITY, OVERALL AVERAGES

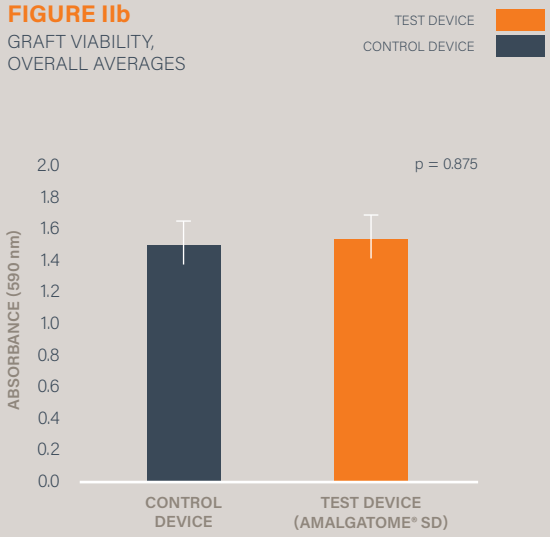
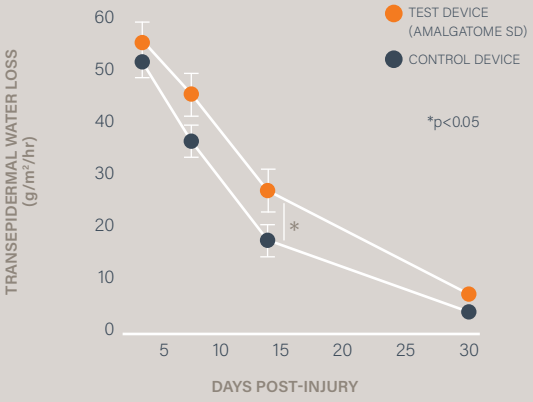
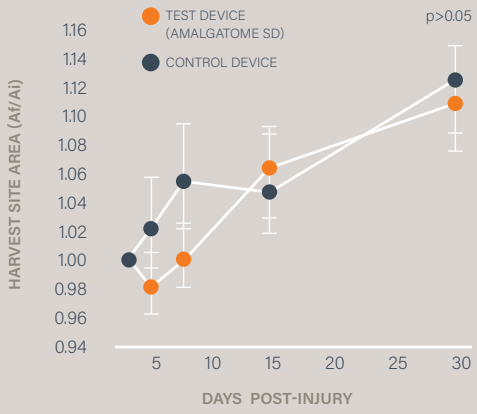


FIGURE III
TRANSEPIDERMAL WATER LOSS AS A FUNCTION OF RE-EPITHELIALIZATION



* Note that the graft thickness is less for test device than for control

FIGURE IV
DONOR SITE CONTRACTION



Visual differences existed with regard to the color of the donor sites. Quantitative assessment of color in the donor sites showed that the control sites tended to be more erythematic than the test device sites (Figure Va) with pigment tending toward hypo-pigmented versus hyper-pigmented as seen in the control sites (Figure Vb). Overall, erythema and pigmentation were significantly reduced at donor sites harvested with the test device (Figure VI).

Biomechanical properties of the donor sites, created with the test device or the control device showed no statistically significant differences with regard to stiffness and percentage of laxity or elasticity (Figure VII).

FIGURE Va

ERYTHEMA PER PIG

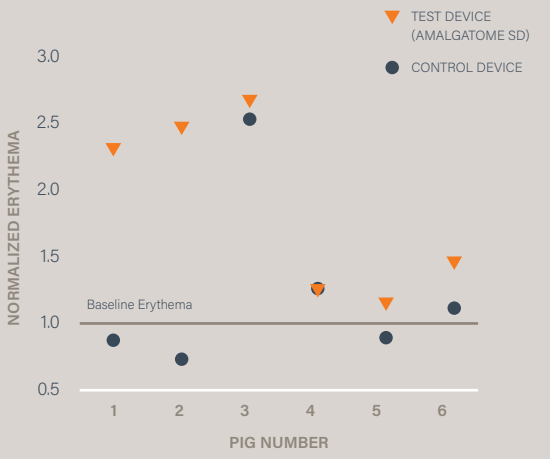


FIGURE Vb

PIGMENTATION PER PIG

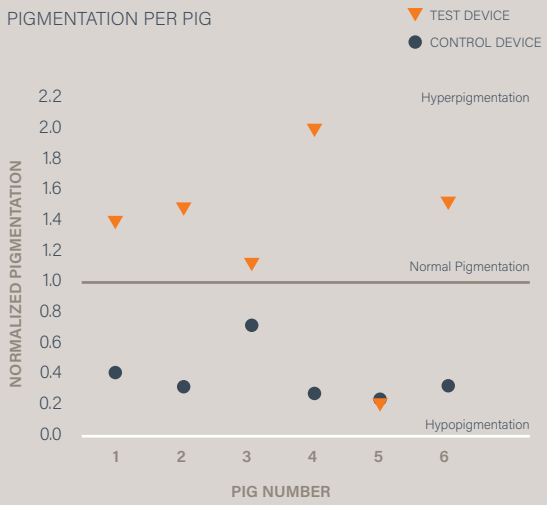


FIGURE VI

DONOR SITE COLOR AS FUNCTION OF DEVICE

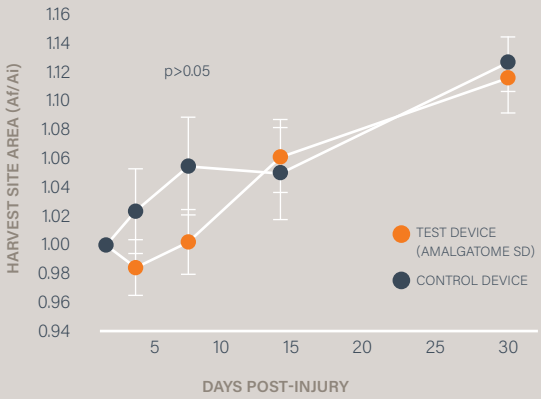


FIGURE VII

DONOR SITE BIOMECHANICAL PROPERTIES

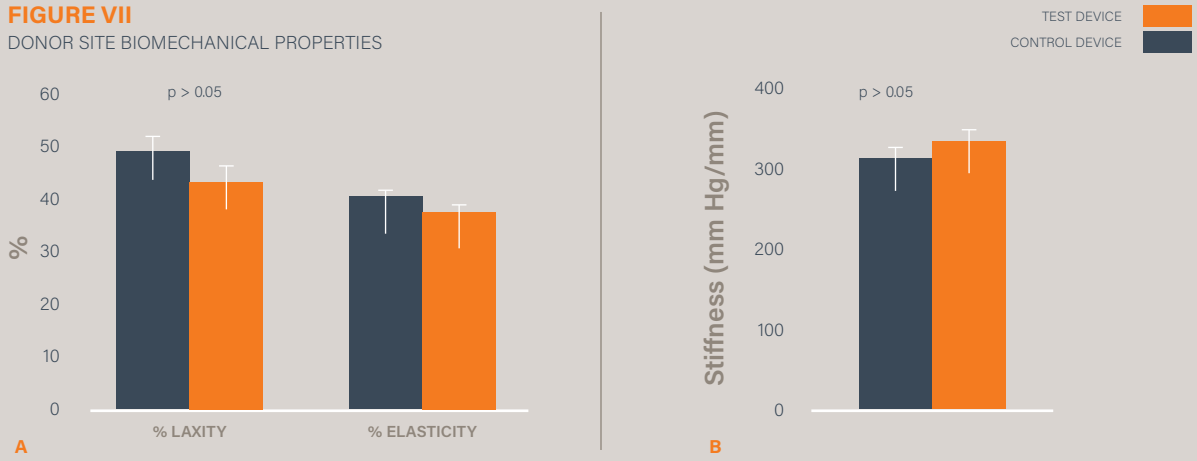
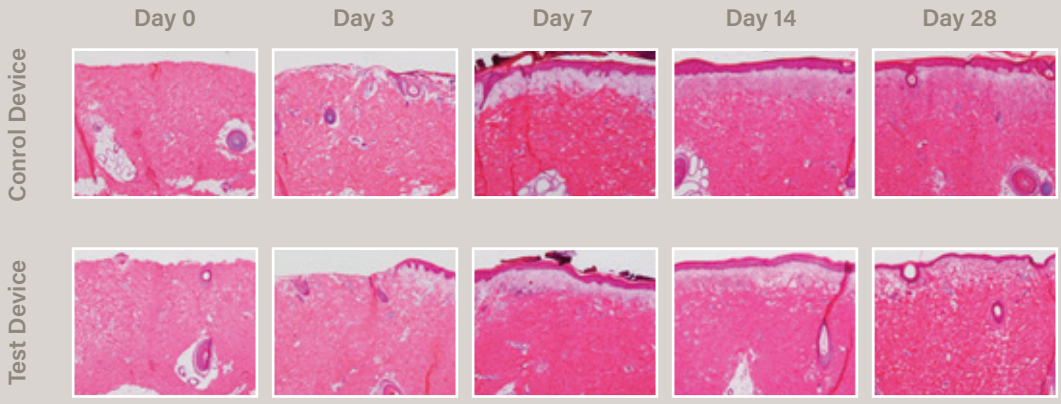


FIGURE VIII

STUDY STSG II



Six mm biopsies, collected throughout the study. Biopsies were frozen at -20° C. Crysections were cut at 7µ thickness, stained with hematoxylin and eosin and imaged using brightfield microscopy.

Both devices excised at similar initial depths. On day 3, re-epithelialization is initiated and at day 7 it is complete. No significant differences in dermal or epidermal structure are observed between the control and test devices.

Discussion

Necrotectomy and the harvesting of STSGs are common procedures in the management of many different types of wounds, including burns. For debridement (necrotectomy), hand-driven dermatomes are the most commonly used, though low-frequency ultrasound and hydrosurgery devices have gained popularity,[6,7] STSGs are harvested using hand-driven or mechanical dermatomes. The proof-of-principles studies described here were aimed at comparing a new type of dermatome with the "standard ones."

Overall results of the STSG trials showed equivalent performance between the Amalgatome® SD and standard dermatomes on a number of clinical and practical aspects. The speed of healing of the donor sites was similar among the different types of dermatomes (both studies) with no substantial difference in visual observation, via histology or via trans-epidermal water loss measurements. Overall graft viability was similar in study STSG II as was overall usability of the harvested grafts. On post-operative day 29, donor site contraction and biomechanical properties (laxity, elasticity, stiffness) of the donor sites were also similar between test and control groups. Erythema and pigmentation were significantly greater when the site was harvested by a traditional dermatome. It should be noted, though, that both pigmentation and erythema of donor sites change over a prolonged period.[22] Thus, the color of the donor sites may return to normal values as the tissue continues to heal and remodel.

In trials Debridement I and STSG I, on STSG harvesting and excision of necrosis respectively, thickness measurements with a calibrated microscope showed better consistency within the test-dermatome excised tissues. Wound healing-related observations (e.g. post-operative erythema, edema) showed similar results and the percentages of development of both granulation tissue and epithelium, as well as the speed of re-epithelialization were also equal, both in debrided wounds and donor sites. In study Debridement I, the use of the test device was subjectively observed to result in less blood loss than when excision was performed with the control device. Histologically, there were no significant differences with regard to aspects of inflammation, fibrosis or healing.

In study STSG I, the test device reached better scores than the control devices on ease of device assembly, overall ease of use, the depth of the debridement as intended by the setting on the depth gauge, consistency of the debridement thickness, maneuverability and the device size.

In study Debridement I, the test device subjectively scored better on the ease of device assembly, the overall ease of use, the depth of the debridement as it was intended by the setting on the depth gauge, consistency of the excised tissues, the device accuracy, and the device size. In neither of study STSG I and debridement did the control devices score better on any of the ease-of-use aspects.

Limitations

The studies described here are small in size. More importantly, although pig skin resembles human skin to a large extent, results in a pig study can only be extrapolated to the human situation to a limited extent. The studies were different in their configuration, but this was done to be able to measure different aspects of STSG harvesting, excision of necrosis, and subsequent aspects of wound healing and quality of the excised tissues.

The results of these studies, however, are uniform and consistent: the test device performed at least equally well on most study aspects when compared to control devices with regard to excision of necrosis and harvesting of an STSG, while the microscopically measured thickness of the test-device-excised tissue was more uniform.

Conclusion

The Amalgatome® SD, a dermatome with a high-speed rotating excision ring, was compared in three pig studies to conventional, powered oscillating-blade-using or manual dermatomes for the excision of necrosis after a burn injury and for the harvesting of a split-thickness skin graft. The new dermatome performance was equal to the control dermatomes on all aspects, studied in all trials with respect to overall healing, including viability of the harvested grafts, time to complete re-epithelialization and biomechanical properties of the donor sites. Although there were statistically significant differences on the level of pigmentation on post-operative day 30, this time point is too early to draw long-term conclusions on that aspect of the results. The test device scored better on consistency of the thickness of the excised tissues, as measured using a calibrated microscope, which is probably the most important aspect of using a dermatome since this may result in better grafts and better outcomes for the recipient wound bed site as well as the donor site.

The test device also scored better on several aspects of usability, including, particularly, maneuverability, which is yet another very important aspect of dermatome usage. While these results were obtained in pig studies, this new device seems to offer some essential improvements over the standard devices, used for harvesting STSGs and for the excision of necrosis. Studies in humans will have to be performed to test for the same parameters.

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