BC3 Technologies

MADE IN THE USA

STOPS BLOOD LOSS FAST.

SEAL

HEMOSTATIC WOUND SPRAY

SEAL Hemostatic Wound Spray

BC3 Technologies has revolutionized wound treatment with its newest product, SEAL Hemostatic Wound Spray. This remarkable spray contains a highly effective form of chitosan, a natural polysaccharide known for its anti-hemorrhagic properties. SEAL has been extensively tested and confirmed to be highly effective in stopping severe bleeding, making it an excellent option for treating wounds that would otherwise be life-threatening. Moreover, using chitosan on traumatic skin lesions can significantly lower the risk of complications, increase the likelihood of survival during the acute healing phase, and ultimately decrease the total cost of treatment. SEAL Hemostatic Wound Spray from BC3 is the reliable solution for severe bleeding wounds.

The properties of SEAL can be summarized as follows:

- Natural biomaterial.
- Highly effective in stopping severe bleeding quickly.
- Acceleration of wound closure.
- Ability to cover complex wound geometries.
- Capability to reach and treat hard-to-access wounds.

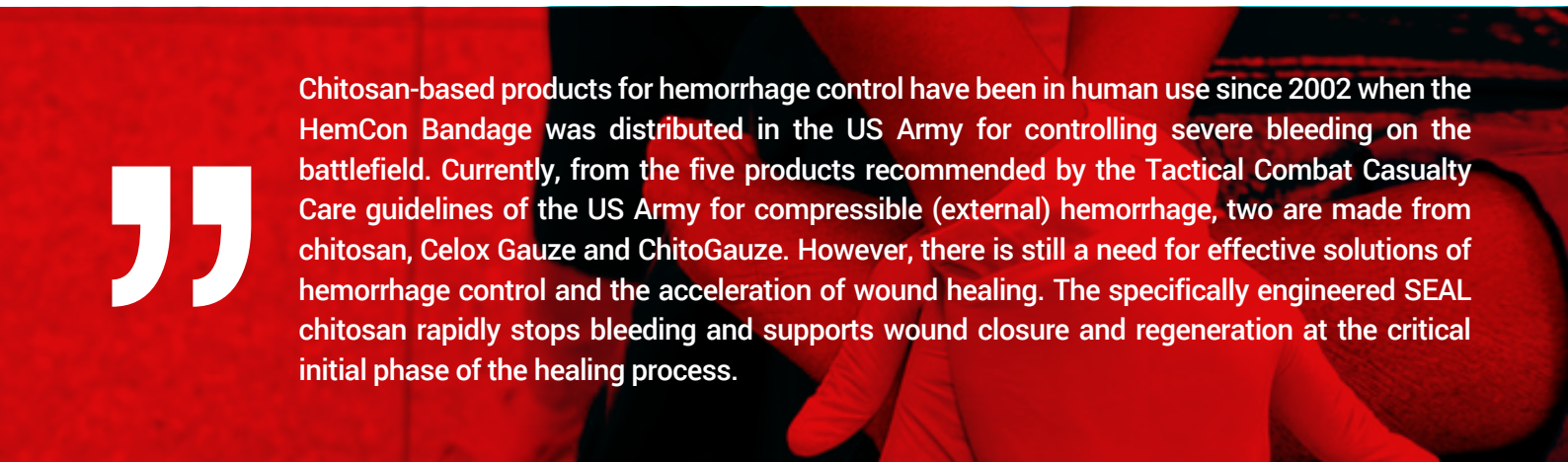
Background

Wound management remains a challenging task. Wound healing involves multiple cell populations, the extracellular matrix and the action of soluble mediators such as growth factors and cytokines. Although the process of healing is continuous, it can be divided into four phases: 1) coagulation and hemostasis, 2) inflammation, 3) proliferation, and 4) remodeling with scar tissue formation. The approach to wound management will effectively influence the outcome of the healing process [1].

Traumatic injuries pose a particular challenge, as a sequence of life-threatening conditions can occur simultaneously, including hemorrhage, impaired resuscitation, shock, inflammation, and coagulopathy. Proper management of a massively bleeding trauma patient requires early identification of the bleeding source, followed by prompt measures to minimize blood loss, restore tissue perfusion, and achieve hemodynamic stability.

The ideal topical product to treat wounds should be biocompatible and nontoxic and be able to enhance healing, without having adverse effects on the natural process of tissue regeneration. Chitosan seems ideal for dermal applications, as it is highly biocompatible, biodegradable, nontoxic, and provides strong hemostatic and antimicrobial properties. Numerous studies have shown the benefit of chitosan during all four phases of the wound healing process, leading to reduced healing times of skin wounds [2,3].

Chitosan is well-known for its potent hemostatic properties that don't rely on any aspect of the typical blood coagulation cascade. Instead, hemostasis is achieved through a combination of linkages (adherence) to red blood cells and tissues, forming a physical barrier around the severed vessels [4].



Chitosan-based products for hemorrhage control have been in human use since 2002 when the HemCon Bandage was distributed in the US Army for controlling severe bleeding on the battlefield. Currently, from the five products recommended by the Tactical Combat Casualty Care guidelines of the US Army for compressible (external) hemorrhage, two are made from chitosan, Celox Gauze and ChitoGauze. However, there is still a need for effective solutions of hemorrhage control and the acceleration of wound healing. The specifically engineered SEAL chitosan rapidly stops bleeding and supports wound closure and regeneration at the critical initial phase of the healing process.

Properties of SEAL

SEAL Hemostatic Wound Spray is composed of chitosan dry powder in spray form that provides a physical barrier or seal to stop the flow of blood. When sprayed on a wound and upon contact with blood or exudate, in combination with manual pressure to the wound, SEAL quickly forms a strong seal that completely covers the wound.

SEAL is available in three different sizes:

Model	Volume
Small **(OTC)**	1.5 oz
Medium	2.5 oz
Large	7.1 oz

SEAL Hemostatic Wound Spray combines two major innovative aspects which are 1) the specific activation of chitosan to yield a particularly potent hemostatic material, and 2) the application as sprayable product.

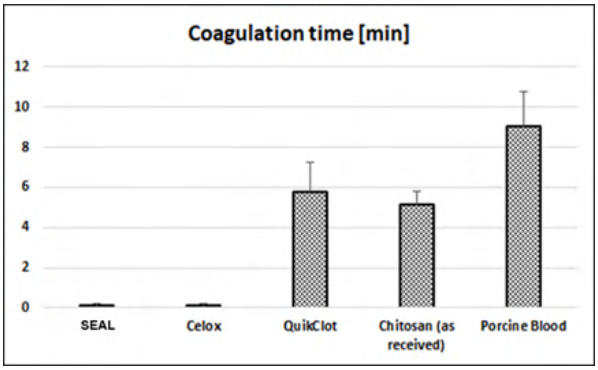
Advantages of SEAL

Key Attribute	SEAL Aerosolized Chitosan	Chitosan Granules	Chitosan Bandages
Rapid, 5-second administration	✓	✓	✗
Ease of use in wind and rain	✓	✗	✓
Deep penetration of Wound Architecture	✓	✗	✓
Ultra-Compact	✓	✗	✗
Touch-free user application	✓	✓	✗
Enables expedited triage process	✓	✗	✗
Use in Low-light	✓	✗	✓

It is well-known that chitosan induces blood clotting by electrostatic interaction between its positively charged glucosamine subunits and negatively charged blood cells. In SEAL, the properties of chitosan are fine-tuned for maximum electrostatic potential and binding capacity towards blood cells.

Testing of SEAL in Porcine Blood (in vitro)

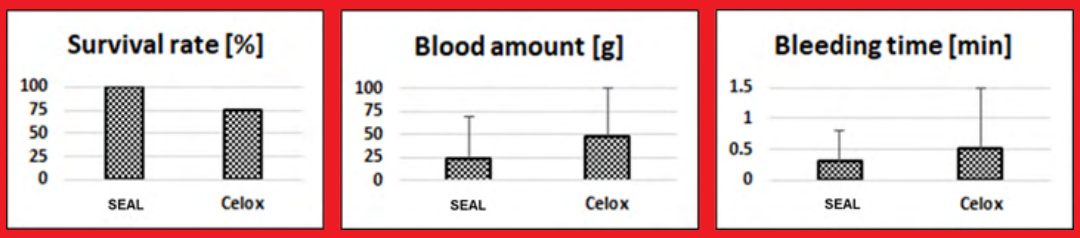
The efficacy of SEAL to stop bleeding has been compared to hemostatic agents used in the military (Celox, QuikClot) by analyzing coagulation times in porcine blood. SEAL and Celox lead to immediate blood clotting. In contrast, with raw chitosan (as received) and QuikClot it takes approx. 5-6 min for blood to coagulate. As reference, porcine blood without hemostatic agent coagulates after approx. 9 min in these experiments.



Coagulation times of porcine blood after addition of hemostatic agents.

Performance of SEAL in Severe Bleeding Model (in vivo).

SEAL was tested against Celox in the swine femoral artery injury model which is the standard model of most severe bleeding for hemostatic agents used in the military. While the mean bleeding time was similar between the two products, post-treatment blood loss was half after treating with SEAL compared to Celox, confirming the high hemostatic efficacy. The survival rate of the SEAL group was 100% and that of the Celox group 75%. Both gross necropsy (full cranial, thoracic and abdominal evaluation) and histopathology of the application site and organs (lung, liver, kidney, and pancreas, among others) did not show any signs of tissue or organ damage related to the application of the product. SEAL proved to be highly efficient and safe.



Survival rate, blood amount and bleeding time of SEAL compared to Celox in severe bleeding model.

Contact

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References

[1] T. Velnar et al., The wound healing process: an overview of the cellular and molecular mechanisms, J Int Med Res 2009;37:1528-42.
[2] R. A. A. Muzzarelli, Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone, Carbohydr Polym 2009;76:167-82.
[3] B. Maldonado-Cabrera et al., Therapeutic effects of chitosan in veterinary dermatology: A systematic review of the literature, Prev Vet Med 2021;190:105325.
[4] B. S. Kheirabadi et al., Evaluation of topical hemostatic agents for combat wound treatment, US Army Med Dep J 2011:25-37.

SEAL – STOPS BLOOD LOSS FAST

SEAL Hemostatic Wound Spray - Summary of Studies

BC3 Technologies' SEAL® Hemostatic Wound Spray is a product developed for application on severely bleeding wounds. SEAL is composed of chitosan powder that provides a physical barrier or seal to stop the flow of blood. When sprayed on a wound and upon contact with blood or exudate, in combination with manual pressure to the wound, SEAL quickly forms a strong seal that completely covers the wound.

BC3 has conducted substantial pre-clinical research regarding the safety and efficacy of SEAL. This included 1) in vitro studies in the presence of porcine blood, 2) testing of the hemostatic efficacy of SEAL under normal and coagulopathic conditions in a swine femoral artery injury model, and 3) a full-thickness porcine wound healing study. In addition to the tests in the animal wound healing model, 4) the product's efficacy and potential for both acute and chronic wound management has been evaluated in a clinical practice under real-world conditions.

1. In vitro Testing

The efficacy of SEAL to stop bleeding has been compared to hemostatic agents used in the military (Celox, QuikClot, HemCon) by analyzing coagulation times in porcine blood. SEAL and Celox lead to immediate blood clotting. In contrast, with QuikClot and HemCon it takes approx. 4-6 min for blood to coagulate. As a reference, porcine blood without a hemostatic agent coagulates after approx. 9 min in these experiments (**Figure 1**).

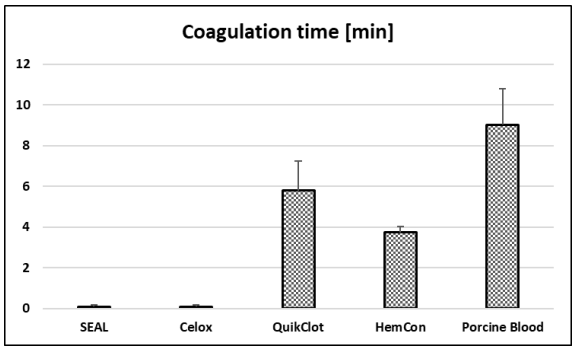

Figure 1. Coagulation times of porcine blood after the addition of hemostatic agents.

Furthermore, since it is well-known that the application of the hemostatic agent QuikClot may lead to thermal tissue injury due to a rapid and significant temperature increase up to 100°C and more in contact with blood (**Figure 2**) [Pusateri et al., J. Trauma 2004;57:555], SEAL has been tested in a set of temperature experiments simulating the application on injured skin. In contrast to QuikClot, no temperature increase has been observed. Due to the evaporation of the propellant, there is a short-term temperature decrease reaching a minimum of 12°C one minute after spraying (**Figure 3**). It is hypothesized that a decrease in temperature may contribute to vasoconstriction further accelerating hemostasis with SEAL.

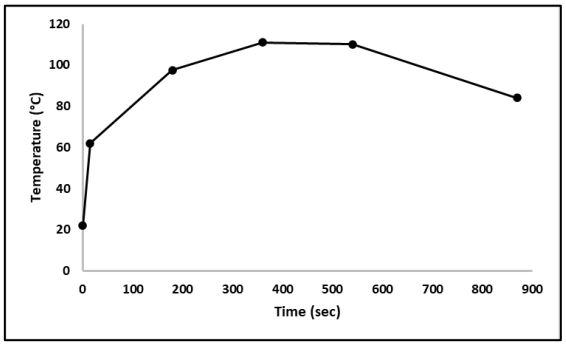

Figure 2. Temperature profile after addition of QuikClot.

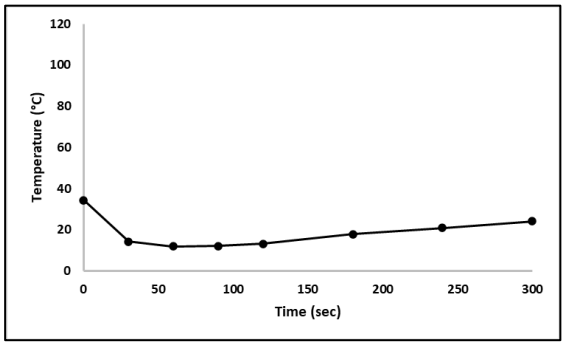

Figure 3: Temperature profile after addition of SEAL.

2. Efficacy in Swine Hemorrhage Model

SEAL was tested against Celox in the swine femoral artery injury model which is the standard model of most severe bleeding for hemostatic agents used in the military (**Figure 4**). While the mean bleeding time was similar between the two products, post-treatment blood loss was half after treating with SEAL compared to Celox, confirming the high hemostatic efficacy. The survival rate of the SEAL group was 100% and that of the Celox group 75%. Both gross necropsy (full cranial, thoracic and abdominal evaluation) and histopathology of the application site and organs (lung, liver, kidney, and pancreas, among others) did not show any signs of tissue or organ damage related to the application of the product. SEAL proved to be highly efficient and safe. See **Attachment 1**.

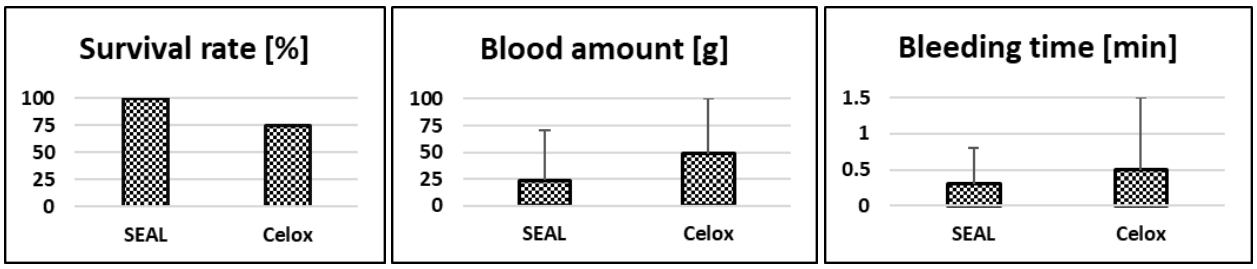

Figure 4: Survival rate, blood amount and bleeding time of SEAL compared to Celox in a swine severe bleeding model.

3. Wound Healing in Swine Model

A full-thickness wound healing study was conducted to evaluate the safety of SEAL compared to Celox, using a standardized pre-clinical model conducted in swine. The study thoroughly evaluated the following attributes: potential effect on the wound healing process, tissue response relevant to the proposed product, chronic inflammation, re-epithelialization, and irritation at the application site.

The collagen synthesis followed the normal patterns and had reached the expected amounts at days 14 and 28. At day 14, the wounds were essentially completely epithelialized, and complete epithelialization of all wounds was observed at day 28. The findings indicate a normal wound healing process (**Figure 5**). See **Attachment 2**.

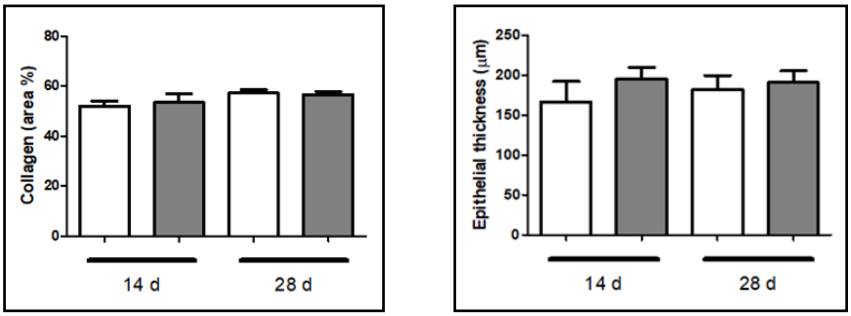

Figure 5: Collagen deposition and thickness of epithelium in the regenerating wound tissue 14 d and 28 d after application of SEAL (gray) vs. Celox in a standardized full-thickness wound model in swine.

4. Management of Acute and Chronic Wounds

A comprehensive evaluation of SEAL under real-world conditions of a clinical wound center was performed by Dr. Brinsley Davids, Advanced Wound Care Practitioner at the Cape Advanced Wound Care Centre (Capetown, South Africa). Dr. Davids confirmed that SEAL has consistently demonstrated an exceptional potential for achieving prompt and effective hemostasis which aligns precisely with the intended purpose (**Figure 6**). Moreover, SEAL's unforeseen benefits in aiding chronic wound healing hint at possible future applications beyond its current scope.

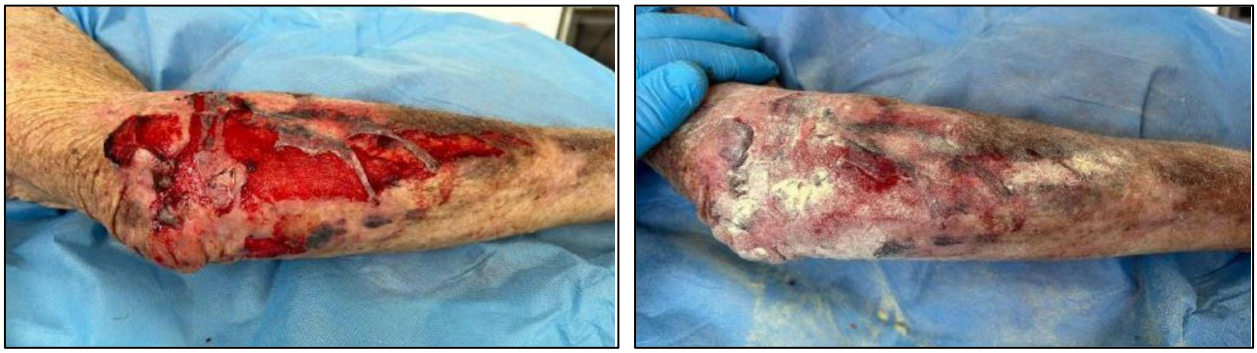

Figure 6: Application of SEAL for immediate hemostasis and effective wound management. Wound closure was observed within 7 days. An iodine-impregnated dressing was applied as secondary dressing.

Attachments

1 - Hemostatic efficacy of SEAL in a swine femoral artery injury model
2 - Study of wound healing in full-thickness wound model in swine

Attachment 1

Hemostatic efficacy of SEAL in a swine femoral artery injury model

1. Purpose

The purpose of this study was to fully demonstrate the safety and efficacy of SEAL Hemostatic Wound Spray and to confirm that it has at least similar performance characteristics in comparison to Celox in a standardized swine preclinical model under normal and coagulopathic conditions.

2. Test Model

The test was conducted according to a published standard swine hemorrhage model for efficacy assessment of topical hemostatic agents, which was previously approved by the US Army Institute of Surgical Research Animal Care and Use Committee (Kheirabadi et al., J. Trauma 2011;71:136). Sixteen adult-castrated male pigs were selected and divided into 4 experimental groups, SEAL (normal animals), SEAL (coagulaopathic animals), Celox (normal animals), Celox (coagulaopathic animals). A 4-mm arteriotomy was made in the femoral artery and free bleeding allowed for 30 seconds. SEAL or Celox were applied to the wounds and compressed with a gauze for 3 minutes. Fluid resuscitation was given to increase and maintain the mean arterial pressure between 60 and 65 mm Hg. Animals were observed for 2.5 hours or until death. See **Figure 1**.

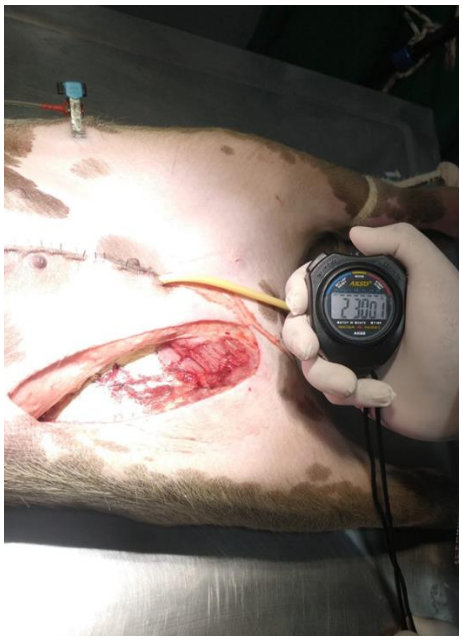

Figure 1: Wound status at 2.5 hours after application of SEAL.

Study end points included bleeding time, blood loss, blood pressure, survival rates and a simulated walking test at the end of the survival time to verify whether rebleeding would occur. Moreover, a potential rebleeding was also investigated after removal of the material at the end of the 2.5 hours or before exsanguination. In addition, a complete blood count with standard clotting tests (PT, APTT, ACT, fibrinogen) was performed before and at the day of the surgery to ensure compliance with the normal range, and that the pigs were healthy enough to undergo the surgical procedures. Besides that platelet counts and other parameters were monitored.

3. Test Devices

Both SEAL and Celox consist of chitosan as hemostatic component. While SEAL is made from a specifically activated form of chitosan binding blood cells to facilitate coagulation, Celox' mode of action is based on the uptake of liquid from the bleeding wound. SEAL has received the FDA clearance in 2022. Celox has received the FDA clearance in 2007 and is until today one of the most widely used products for hemostatic applications.

4. Results

4.1. Bleeding Time

The mean bleeding times of all test animals (normal and heparinized) are without statistically significant differences between the SEAL and the Celox groups. The SEAL group has been shown to repeatedly control external bleeding in heparinized animals, which is equivalent to the Celox group. The mean bleeding times of the normal animals are very low for both devices (SEAL: 0.3 ± 0.5 min, Celox: 0.5 ± 1.0 min; see **Figure 2**), confirming their high hemostatic efficacy.

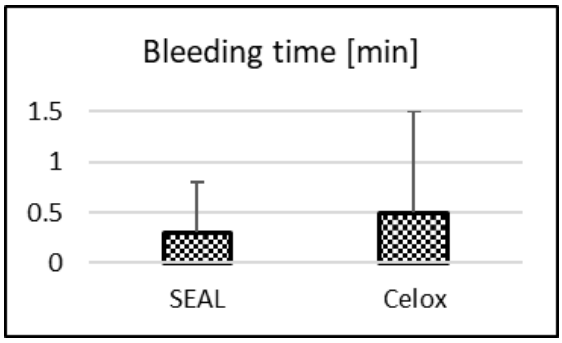

Figure 2: Bleeding time of SEAL compared to Celox.

4.2. Blood Loss

Similar to the bleeding times, the analysis of the mean post-treatment blood loss revealed no statistically significant differences between the SEAL and the Celox groups. There is a trend towards lower blood loss in the normal (non-heparinized) animals of the SEAL group (23.6 ± 46.4 ml) compared to the Celox group (48.4 ± 52.1 ml) (see **Figure 3**), although statistically not significant.

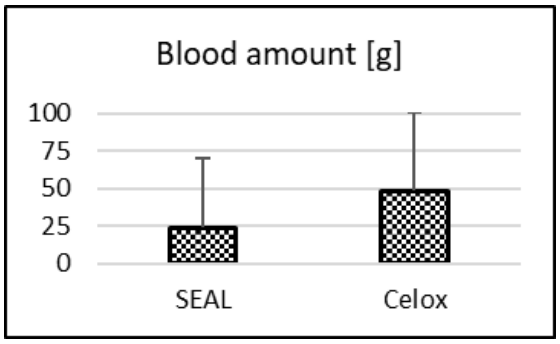

Figure 3: Amount of blood loss of SEAL compared to Celox.

4.3. Arterial Pressure

The mean arterial pressure was similar and without statistically significant differences between the SEAL and the Celox groups at the end of the 2.5 hours observation period, confirming sufficient blood flow to vital organs.

4.4. Survival Rate

The survival rate of the SEAL group was 100% and that of the Celox group 75% for the normal (non-heparinized) animals. All of the coagulopathic animals survived the 2.5 hours post-treatment observation period. The 100% survival of the animals treated with SEAL confirms the high efficacy of the device to stop bleeding and the support of sufficient blood pressure in the post-treatment period.

4.5. Post-Surgical Bleeding

In a simulated walking test (flexing and stretching of the treated legs) at the end of the 2.5 hours observation period, none of the animals in both device groups showed signs of bleeding, confirming the stability of the hemostasis produced by SEAL and Celox.

After removal of the hemostatic material at the end of the study, bleeding occurred in 25% of both the SEAL and Celox groups of normal (non-heparinized) animals. Remarkably, only 50% of heparinized animals showed signs of bleeding after removal of SEAL while 100% of heparinized animals were bleeding again after removal of Celox. This observation confirms the efficient control of external bleeding with the application of SEAL also in heparinized animals, simulating coagulopathic conditions.

5. Conclusions

A rigorous hemorrhage model was conducted in swine (normal and coagulopathic animals) and confirmed that SEAL was able to achieve hemostasis, with no statistically significant differences between SEAL and Celox in bleeding/hemostasis time (time period necessary for bleeding to stop), blood loss, post-treatment blood loss, mean arterial pressure, survival time, and percentage survival. The blood parameters that were monitored showed no abnormalities. Moreover, both gross necropsy and histopathology did not show any signs of tissue or organ damage related to the application of the device. In addition, thromboemboli have

not been developed in the surrounding tissues or other areas, and the risk of a thromboemboli migration to critical structures was also ruled out. No residues of the product were found in the analyzed samples. The study results lead to the conclusion that SEAL has at least similar performance characteristics as Celox.

Reference

Final study report "Efficacy Assessment of SEAL – Pig study", Report # N.2381211.2022, Ecolyzer Laboratories (Resende/RJ, Brazil), 23rd May 2022.

Attachment 2

Study of wound healing in full-thickness wound model in swine

1. Purpose

The objective of this study was to evaluate the safety of SEAL Hemostatic Wound Spray compared to Celox, using a standardized pre-clinical model conducted in swine. The following parameters were evaluated: potential effect on the wound healing process, tissue response to the product, chronic inflammation, re-epithelialization, and irritation at the application site.

2. Test Model

The study was conducted using a full-thickness excisional wound model in swine. Two groups were formed for this study, SEAL and Celox. Each animal received 8 wounds (2.5 x 2.5 cm) of full thickness by excision of the skin to the fascial plane using a scalpel (4 wounds in the dorsal cranial portion and 4 wounds in the dorsal caudal portion) that were randomly distributed to receive treatments with SEAL (4 wounds) and Celox (4 wounds). The products were administered topically as provided by the manufacturers (**Figure 1**).

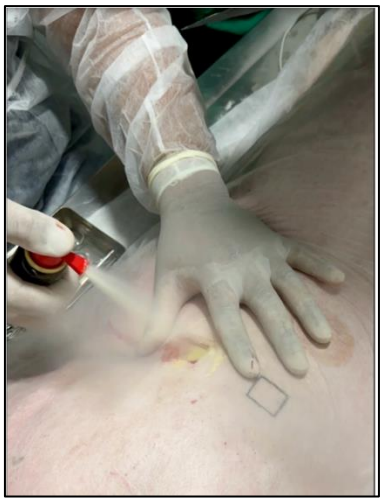

Figure 1: Application of SEAL on full-thickness excisional wound (2.5 x 2.5 cm) in swine.

During the study, the animals were subjected to weighing, the surgical procedure (experimental induction of wounds), application of the test items (SEAL and Celox), daily photographs of the wounds (at the time of daily dressing change), washing of the wounds every second day, daily observation of wounds (visual inspection), euthanasia and necropsy (collections for histopathological examination). The wound healing progress was monitored for up to 28 days, with biopsy samples from the wound sites collected 14 days and 28 days after treatments and sent for histopathological evaluation.

3. Test Devices

Both SEAL and Celox consist of chitosan which implies a similar impact on the wound healing process.

4. Results

4.1. Visual Inspection

The visual inspection showed that the wound healing process presented the same pattern for all wounds regardless of the product (SEAL or Celox) used to fill the wound cavity. No pus was identified in any of the wounds. Minor bleeding was observed in a few cases during the healing process with no difference between the SEAL and Celox groups. Irritation and/or inflammation of all wounds (regardless of the groups) were observed during the visual inspections only in the first three days which can be considered an indication that the wound healing process followed the normal course. In accordance with scientific literature, the inflammation in the normal skin wound healing process usually lasts for 2–5 days. In conclusion, the visual inspections indicated that SEAL and Celox had a similar impact on the wound healing process.

4.2. Collagen Synthesis

Collagen, being the most abundant protein in the composition of the extracellular matrix, plays an important role in wound regeneration, and collagen synthesis, degradation and tissue deposition occur simultaneously throughout the healing process. During the evaluated experimental period (14 and 28 days) the skin wounds exhibited the expected collagen deposition in their beds, as determined after histological staining with Gomori's Trichrome, where the collagen fibers are stained with a blue color.

Qualitatively, the wounds in both groups showed an adequate deposition and organization of collagen fibers, as evidenced by representative photomicrographs. At 14 days, the average values of area occupied by collagen reached the expected amount (about 50%) as described in the literature. After 28 days, there was no statistically significant difference between the SEAL and Celox groups and also compared to 14 days, leading to the conclusion that the collagen synthesis process had reached a stationary phase, approaching 60% occupancy which is similar to values described in the literature. See **Figure 2**.

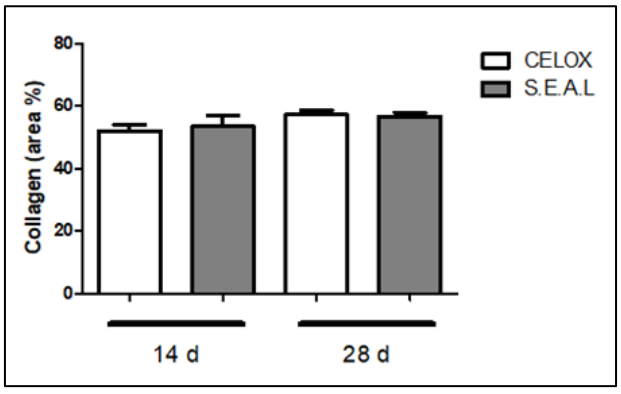

Figure 2: Collagen deposition in the regenerating wound tissue.

4.3. Epithelialization

The epithelialization phase plays a unique role during the wound healing process since the intact epithelial tissue is both a barrier against external aggressions and a protection against electrolyte and water loss. The absence of epithelium exposes internal tissues to excessive solar radiation, foreign bodies, contamination and consequent bacterial and fungal infections, among others.

The evaluation of the average thickness of the epithelial layer in both experimental groups revealed that the re-epithelialization process was aligned to the deposition of collagen. Although it is possible to observe a slight tendency towards greater epithelial thickness in the wounds treated with SEAL, there was no statistically significant difference to the Celox treatment. At 14 days, the wounds were already essentially completely epithelialized, and complete epithelialization was observed at 28 days. See **Figure 3**.

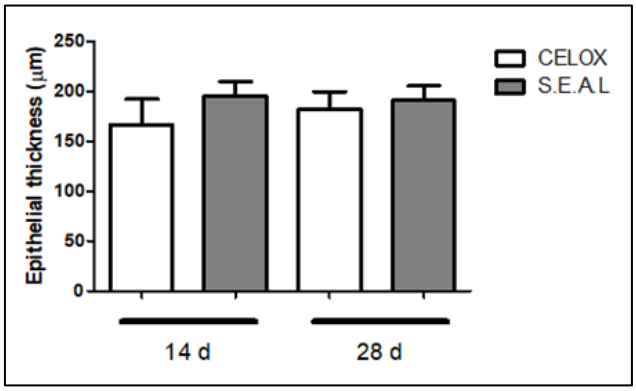

Figure 3: Thickness of epithelium in the regenerating wound tissue.

4.4. Tissue Reaction

Skin fragments analyzed macroscopically from all animals presented an outer surface that was rough, hairy and cream-colored, with a central depression in all animals; the animals with lesions of 14 days sometimes presented a central crust of up to 2.5 cm, sometimes erosion, with a thin margin of scar tissue; the animals with 28 days old lesion showed a central focus of millimetric crust surrounded by an extensive margin of scar-like tissue. The surgical face showed tissue from the muscle type in all samples. The consistency of cuts was smooth in all fragments. The cut surface was pinkish-cream compact, sometimes with a brownish linear line corresponding to the wound site.

The presence of large crusts in the 14-day lesions, as well as the consequent decrease in its extension observed in the 28-day lesions, associated with the progressive increased margin of scar-like tissue show that the process of regeneration of the wounds occurred as expected both in the wounds treated with SEAL as with Celox. No macroscopic and microscopic differences were observed in the appearance of the lesions. The findings indicate a normal wound healing process in both groups.

The semi-quantitative evaluation to assess tissue reactivity confirmed the similar wound healing process following treatment with SEAL or Celox. Differences were minor between the groups and not statistically significant. In addition, there is a trend of decreasing reactivity from day 14 to day 28, although the differences between the time points are without statistical significance.

5. Conclusions

From the daily visual inspections of the wounds that received SEAL or Celox it can be concluded that both products have the same impact on the wound healing process. There was no difference visible in the presence of pus, irritation, inflammation or bleeding.

In addition, the analysis of the percentage of collagen and thickness of epithelium in the regenerating wound did not show any difference when comparing the SEAL and Celox groups.

The macroscopic reaction was not significant and similar for SEAL and Celox. The findings indicate a normal wound healing process in both groups. The histopathological semi-quantitative evaluation to assess tissue reactivity confirmed the similar wound healing process following treatment with SEAL or Celox. There were no statistically significant differences between the groups at both time points day 14 and day 28. In addition, there was a trend of decreasing reactivity from day 14 to day 28, although without statistical significance.

From the results of the study it can be concluded that SEAL is as safe as Celox when applied on wounds and that both devices have the same impact on the wound healing process.

Reference

Final study report "Safety assessment in the healing process of wounds with the SEAL product in pigs - Topical route", Report # N..2854615.2022, Ecolyzer Laboratories (Resende/RJ, Brazil), 19th Dec 2022.

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