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Comparison of wound-bursting strengths and surface characteristics of FDA-approved tissue adhesives for skin closure

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Abstract—We compared the wound-bursting strength (WBS), mode of adhesive failure and surface characteristics of two FDA-approved tissue adhesives for skin closure in an incisional rat model using a randomized, controlled, blind animal experiment. Standardized 2-cm full-thickness incisions were made in duplicate on both sides of 15 rats and closed with Indermil, or High Viscosity Dermabond (HVD) following manufacturers' instructions. WBS was measured 5 min later with a validated commercial instrument. Wound sections were also observed under light and scanning electron microscopies. Indermil was significantly weaker than HVD (mean difference, 143 mmHg; 95% CI, 42–229 mmHg, $P = 0.002$). The mode of failure for Indermil was primarily cohesive in the adhesive and the primary failure mode for the HVD was interfacial (χ^2, $P < 0.01$). Microscopic observations demonstrated that application of HVD resulted in a thick, uniform and smooth surface while Indermil resulted in a thin, irregular, cracked surface. We conclude that HVD is stronger, thicker and more uniform than Indermil.

Keywords: Octylcyanoacrylate; tissue adhesive; bursting strength.

1. INTRODUCTION

Cyanoacrylate tissue adhesives have been available for wound closure for over half a century [1]. Currently, the only FDA approved topical skin adhesives include a butylcyanoacrylate (Indermil™, US Surgical, Norwalk, NJ, USA), a low viscosity octylcyanoacrylate (Dermabond® Topical Skin Adhesive, Ethicon, Somerville, NJ, USA) and a high viscosity octylcyanoacrylate (High Viscosity Dermabond®, Ethicon). Multiple clinical trials have demonstrated that lacerations and surgical

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incisions closed with topical skin adhesives have similar outcomes as those closed with standard wound closure methods [2–4].

When choosing a tissue adhesive for wound closure, the clinician must be confident that the adhesive is strong enough to hold the wound edges together, thus minimizing the risk of dehiscence. Thus, an important characteristic of tissue adhesives that contributes to a clinician's preference in choosing a particular adhesive is their wound-bursting strength (WBS). With the introduction of several new tissue adhesives we felt that it was important and timely to determine their relative strength. We, therefore, compared WBS of the approved adhesives in surgical incisions in rats. We also compared their surface characteristics in this wound model.

2. METHODS

2.1. Study design

A randomized experiment was conducted to compare the wound-bursting strength of tissue adhesives in rats. This project was approved by the Institutional Animal Care and Use Research Review Board.

2.2. Animals and setting

This study was conducted in the animal research laboratory of a university-based emergency department. Fifteen young female Long Evans rats, weighing 250–350 g, were used in this study. The rat was chosen, since it has been well-described in prior incisional WBS studies [5–7]. Animals were given a standard diet *ad libitum* several days prior to the investigation and were fasted overnight before any procedures. Housing and care for animals was in accordance with the National Research Council guidelines [8].

2.3. Experimental protocol

All animals tested were anesthetized with an intra-peritoneal injection of a mixture of ketamine hydrochloride (100 mg/ml) and xylazine hydrochloride (20 mg/ml). Additional increments of 0.01–0.02 ml were administered as deemed necessary if the initial dose did not produce the desired level of surgical anesthesia.

Following anesthesia, the hair on either side of the body over the entire dorsal and dorsolateral aspects was clipped and a depilatory lotion (Nair Lotion Hair Remover with Aloe and Lanolin, Carter Products, New York, NY, USA) was spread over the clipped area onto the skin and left for 5 min. The area was then washed with wet cotton and dried with a gauze sponge. Povidone-iodine was applied to the surgical site and then wiped off with a tissue. Isopropyl alcohol (70%) was then applied.

Each rat had two surgical skin incisions created, one on the right side and one on the left side. Each rat was assigned to receive wound closure with Indermil on one

side and High Viscosity Dermabond (HVD) on the other side. The order of adhesive application was determined using a computer-generated randomization schedule.

A straight-line ruler template and a surgical skin-marking pen were used to mark a symmetric 2-cm longitudinal incision over the dorsolateral flank area. Using a #15 blade scalpel, the longitudinal incision was then made along the marking. The incision extended through the skin, subcutaneous tissue and panniculus carnosus. Next, the wound edges were apposed with gloved fingers. The tissue adhesive was then applied topically to the incision as per the randomization schedule. The HVD was applied as three layers according to manufacturer's instructions. The investigator waited approx. 30 s between applications. Manual apposition of the wound edges was maintained for 60 s after applying the final layer. One layer of the Indermil was applied in a spot welding manner as per the manufacturer's instructions. Due to its low viscosity, the application of the Indermil usually resulted in a thin continuous layer.

Full-thickness biopsies were taken from the center of representative glued wounds using a 4-mm surgical punch (Miltex Instrument, Lake Success, NY, USA). The biopsies were taken 1 h after application of the adhesive for histopathological evaluation by a board-certified dermatopathologist blinded to treatment assignment.

The primary outcome was the wound-bursting strength in mmHg (1 mmHg = 133.32 Pa). WBS was measured using a previously validated method and instrument [6]. The instrument used for testing incisional strength was an in-vivo Biomechanical Test System (BTC-2000™, Surgical Research Laboratories, Nashville, TN, USA). For testing incisional strength, a cyanoacrylate glue (Elmer's Instant Krazy Glue–All Purpose, Elmer's Products, Columbus, OH, USA) was used to bond a grooved plastic ring (2.5-cm internal diameter) around the surgical site. Fombulin Perfluorinated Grease (Ausimont) was then applied to the groove to assure a tight vacuum seal. Upon completion of the cure time of the adhesive (5 min after final layer application), a plastic vertical tube on the instrument was lowered onto the groove and sealed over the ring. Calibrated laser targets were then applied to both sides of the wound through the vertical tube to the exposed skin. A vacuum was then applied to the incisional site until the adhesive layer either split or pulled away from the skin (dehiscence). The failure mode (split (cohesive) or peel (interfacial)) was then recorded. Displacement of the laser targets was captured by the video camera. Time-synchronized data on target/wound deformation and pressure were collected by a computer. The maximum pressure (burst pressure) was then recorded on the test record sheet. This method provides data with less variation than a standard tensiometer, or an air insufflated positive pressure device [6].

We also compared the surface characteristics of the adhesives using light microscopy and scanning electron microscopy. Oil red O and Sudan black stains of frozen sections were used to demonstrate the presence of the cyanoacrylate adhesive [9].

2.4. Data analysis

WBSs are expressed as means and standard deviations and are compared with a paired t-test. The proportion of wound failures due to peel or split of the adhesive are expressed as percent frequency of occurrence and are compared with χ^2 tests. A sample size of 15-paired incisions in each group was chosen in order to have a 90% power to detect a 75-mmHg difference between the groups [10]. We felt that a smaller difference in bursting strength would not be clinically relevant.

3. RESULTS

3.1. WBS

We evaluated 30 incisions in 15 rats. Mean bursting strengths (±SD) were 358 ± 136 mmHg for HVD and 215 ± 90 mmHg for Indermil (Fig. 1). Indermil was significantly weaker than the 3-layer HVD (mean difference, 143 mmHg; 95% CI, 42–229 mmHg, $P = 0.002$). The mode of failure for Indermil was cohesive in the adhesive in 86% of the wounds and interfacial in the remaining 14%. In contrast, the failure mode for HVD was interfacial in 86% of the wounds and cohesive in the adhesive in only 14% of the wounds. The difference in the proportion of cohesive failures between the two adhesives was significant (χ^2, $P < 0.01$).

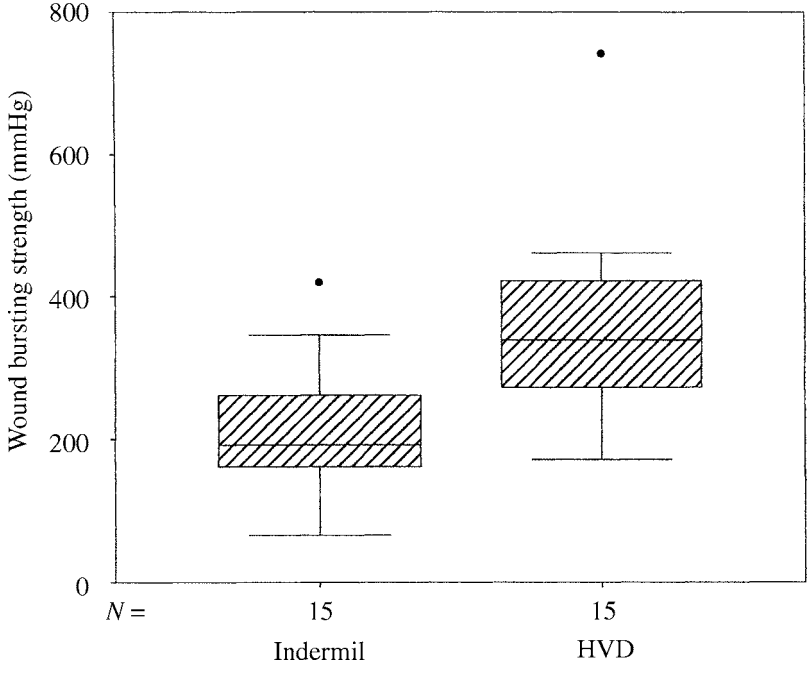

Figure 1. Box plots of bursting strength by type of adhesive. The middle bar is the median and the box describes the inter-quartile range. The whiskers approximate the 95% confidence intervals. Outliers are indicated by the individual points. N denotes sample size.

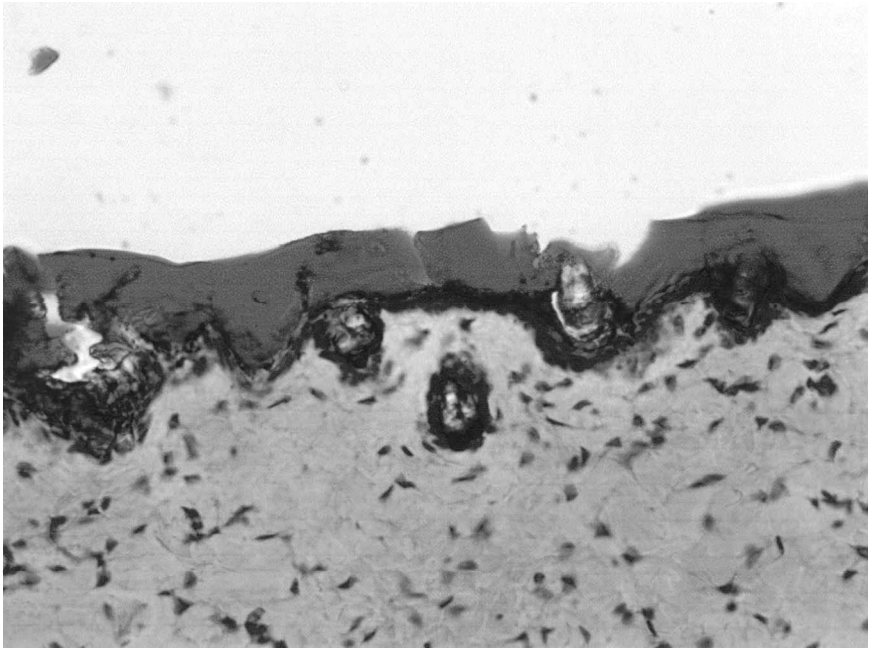

Figure 2. Light microscopy photograph of wound closed with HVD (Oil Red O staining, magnification ×20). Note the thick smooth outer layer of HVD covering the entire wound surface.

3.2. Adhesive surface characteristics

Observation of wound sections from incisions closed with HVD under light microscopy demonstrated a thick (300–500 μm) uniform layer of the adhesive (Fig. 2). In contrast, Indermil's surface was thin (<50 μm) and irregular, with some wound surfaces without any adhesive coverage (Fig. 3).

Observation of wound sections closed with HVD under scanning electron microscopy demonstrated a relatively smooth and regular surface with few shallow (1–3 μm) cracks (Fig. 4). In contrast, Indermil's surface appeared irregular with multiple cracks of varying depths (Fig. 5).

4. DISCUSSION

Each year over 8 million lacerations [11] and 80 million surgical incisions [12] are closed in the USA alone. While most wounds are closed with sutures, the role of topical skin adhesives is expanding. The choice of a specific adhesive for closing wounds must take into account several characteristics including strength, flexibility, microbial barrier function, water permeability and cost. Unfortunately, there is no clinical trial directly comparing HVD and Indermil. As a result, clinicians must base their adhesive preference on mechanical characteristics and cost. At the present time the cost of the two adhesives studied is similar. The results of the current

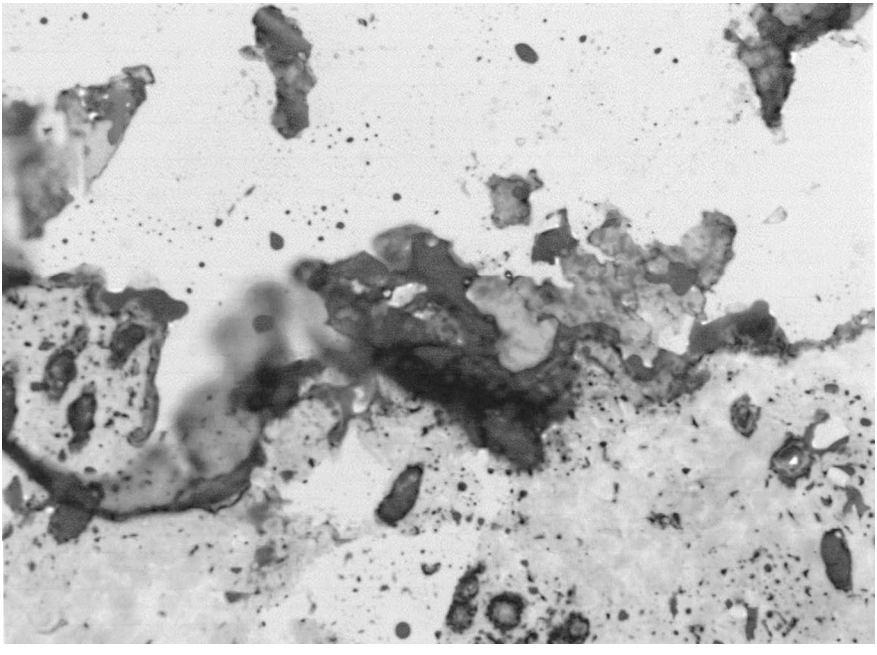

Figure 3. Light microscopy photograph of wound closed with Indermil (Oil Red O staining, magnification ×10). Note the thin irregular outer layer of Indermil, with several wound areas without adhesive coverage.

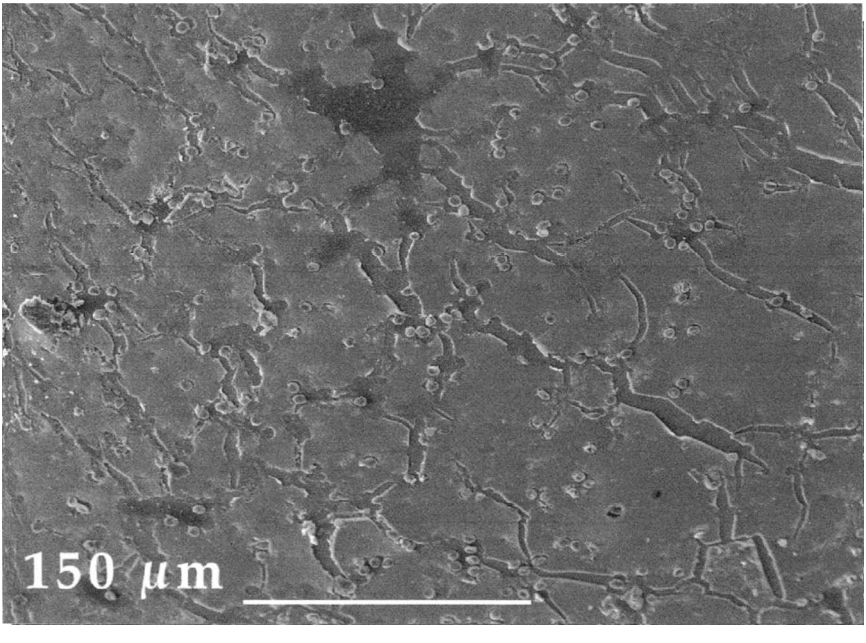

Figure 4. SEM micrograph of wound closed with HVD (magnification ×200). Note the presence of few superficial cracks.

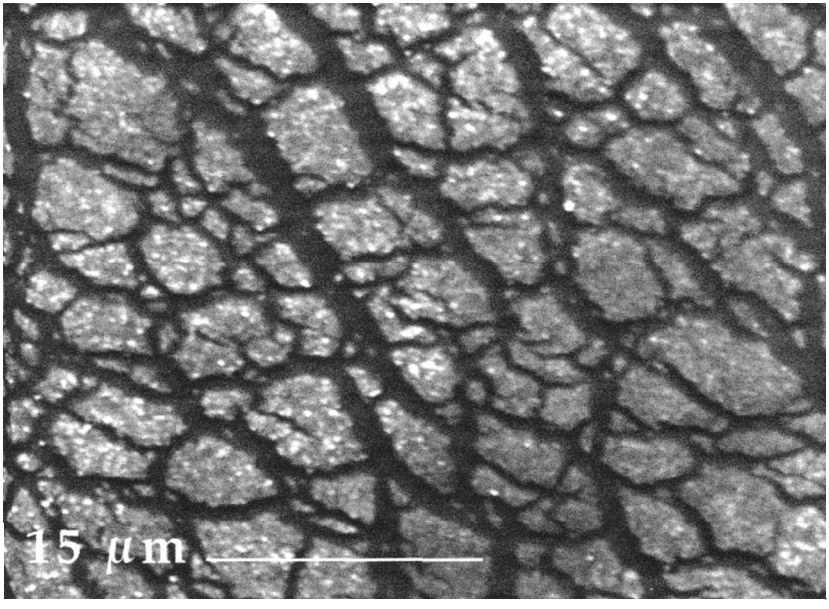

Figure 5. SEM micrograph of wound closed with Indermil (magnification × 2000). Note the presence of multiple cracks.

study demonstrate that the new HVD is significantly stronger than Indermil. This is demonstrated by the higher WBS measured with wounds closed with HVD. In addition, the greater bursting strength of HVD explains its tendency to peel off (interfacial failure) before splitting (cohesive failure); in contrast, Indermil tended to split. While it is unclear how much strength is needed to avoid wound dehiscence, it is reasonable that the greater the bursting strength the more secure the wound closure is. In addition, beyond a certain level of strength the adhesives would peel off the skin owing to the limited cohesiveness of the layers of the epidermis.

A prior study comparing the bursting strengths of low viscosity Dermabond and a butylcyanoacrylate different than Indermil (Histoacryl Blue, Braun, Melsungen, Germany) found that the octylcyanoacrylate was 3-times stronger than the butylcyanoacrylate [13]. These results highlight the differences in tensile strength between the cyanoacrylates. It is also possible that the adhesives were applied in a different manner than in our study, resulting in different bursting strengths. Our method of application was similar to the clinical scenario.

The current study also demonstrates that while Dermabond application creates a thick, smooth and uniform layer, application of Indermil results in a thin irregular surface with multiple cracks. This difference in microscopic surface characteristics may explain the observation that Indermil forms a brittle film while Dermabond forms a flexible one. The presence of multiple cracks and irregularities within the surface of the Indermil adhesive film could also potentially serve as a portal of entry for bacteria and infection.

Multiple methods have been used to determine the strength of healing wounds. The strength of excised wounds was originally measured by attaching them to a standard thread-testing machine [14]. Tension to the tissue on both sides of the wound was sequentially increased until the wound disrupted. A simple test of wound strength was described by Bourne [15] in which excised pieces of skin bearing the wound were hung onto the top of a rack by one end and weights were attached to the free end until wound disruption. Tensile strength is defined as the load per unit cross-sectional area at wound disruption. Breaking strength is the load required to break a wound and does not account for wound geometry. In contrast, WBS refers to the three-dimensional force required to disrupt wounds *in situ*. The advantage of measuring bursting strength is that from a clinical or practical standpoint, clinicians are most interested in the force required to disrupt an actual *in vivo* wound. Methods that measure the force required to break excised wounds may be less representative of the clinical scenario since *in vitro* techniques require tissue excisions. The excision of wounds may disrupt subcutaneous attachments or fibrin deposits that contribute to wound strength. As a result, we chose to measure wound bursting strength in the current study.

Bursting strengths were measured 5 min after adhesive application even though the curing of adhesives may last longer. Thus, it is possible that WBSs would have differed if measured at other points in time. However, we felt that our experiment was most reflective of the clinical scenario where patients are allowed to leave several minutes after wound closure, exposing them to the risk of dehiscence before adhesive curing is complete.

We applied both adhesives following the instructions in the package inserts. Due to its higher viscosity and multiple layering, HVD is thicker than Indermil, which might be responsible for some of the differences in the adhesive's strength. However, according to the manufacturer, Indermil should only be applied in a thin layer, since thicker applications can result in an exothermic reaction with the risk of injury. Finally, it is unclear how our results would be applicable to humans in which the skin is much thicker.

5. CONCLUSIONS

Our study of wound-bursting strength of surgical incisions in rats demonstrates that HV Dermabond adheres better than Indermil. It further shows that the adhesive film of HV Dermabond is thicker and more uniform than that of Indermil. The clinical relevance of these findings remains to be seen.

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