Retinoids are commonly prescribed for a variety of dermatologic conditions, including acne, hidradenitis, and rosacea. At times, these conditions require surgical intervention for both acute and chronic disease management. Within the plastic surgery community, it is widely believed that waiting a minimum of 6 to 12 months after patient cessation of systemic retinoid therapy is necessary before proceeding with elective surgical intervention. This recommendation is based on the theory that retinoids adversely affect wound healing by causing delayed healing, the development of excess granulation tissue, or hypertrophic scarring.

In May 2008, a 28-year-old woman with severe hidradenitis suppurativa that was refractory to medical treatment was referred to the Department of Plastic Surgery at the Medical College of Wisconsin in Milwaukee, Wisconsin.

The patient had multiple areas of involvement, including the scalp, axillae, inframammary folds, labia, perineum, and gluteal folds, the most severe being the right axilla and left inframammary fold (Figure 1A,D). She was referred by her dermatologist due to disease progression with chronically active lesions, purulent drainage, and a history of multiple incision and drainage procedures for abscesses. At the time of her initial visit, she had been receiving isotretinoin...
therapy for 24 months. We initially recommended that she discontinue isotretinoin for at least 6 months prior to surgical treatment; however, the extensive nature of her condition was significantly limiting her normal activities of daily living, compromising her ability to work, and resulting in frequent physician and emergency room visits. For these reasons, the patient and her dermatologist requested more urgent surgical treatment. After performing an extensive literature search that revealed only Level 5 evidence on the topic of isoretinoids and wound healing, we performed a wide excision of the right axillary and left inframammary hidradenitis just 4 months after the patient

Figure 1. (A) This 28-year-old woman presented with severe hidradenitis suppurativa. An area of intractable right axillary hidradenitis is shown, with extensive active disease and frank purulent drainage. (B) Excision of right axillary hidradenitis with healing by secondary intention, 3 weeks postoperatively. (C) Right axilla is shown 20 months postoperatively, with complete healing by secondary intention and acceptable scarring. (D) A second area of hidradenitis was noted in the inframammary region. (E) Excision of hidradenitis on the left inframammary fold with healing by secondary intention, 3 weeks postoperatively. (F) Left inframammary fold is shown 20 months postoperatively, with complete healing and acceptable scarring.
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ceased therapeutic doses of isotretinoin. The wounds were allowed to heal by secondary intention and are shown at 3 weeks postoperatively and after complete healing in Figure 1. The surgical wounds healed unremarkably within 3 months, with no loss of function, relief of all symptoms, and elimination of all signs of disease within the affected area. She subsequently underwent excision of the remaining areas of hidradenitis on the scalp, left axilla, genitalia, and gluteal folds. All healed unremarkably by secondary intention. No hypertrophic scarring or delayed epithelialization was observed. This has also been our clinical experience with hidradenitis patients who have not been receiving isotretinoin and demonstrates the need for more conclusive, data-driven information regarding the effect of isotretinoin on wound healing. Therefore, we investigated in a porcine model the healing of both partial- and full-thickness wounds after treatment with systemic isotretinoin.

METHODS

Following approval from the Institutional Animal Care and Use Committee at the Medical College of Wisconsin, 2 mature sibling Hanford miniature pigs were obtained. After an acclimation period of 4 days, 1 pig was treated with isotretinoin at a dose of 2 mg/kg/d, administered orally along with pig feed over a 60-day period; the other (control) pig received only pig feed over the same time period. The treated pig received a cumulative dose of approximately 120 mg/kg, which is accepted as within safe limits for isotretinoin treatment.6,7 Lipid and liver function panels were monitored in the treated animal by performing a baseline blood draw prior to drug administration and repeating the panels every 1 to 2 weeks during drug administration. The same tests were run on the control animal. Both animals were housed in individual, smooth-sided stainless steel cages at the college’s animal research facility for the entire study period (60 days of treatment followed by surgery and 28 days of wound healing).

Standard-sized partial- and full-thickness wounds were made on each animal 4 days (chosen arbitrarily) after the completion of drug treatment. The procedures were performed under general anesthesia. Using a template, a grid of 24 squares (2.0 × 2.0 cm) spaced 1 cm apart was marked on the right and left flanks of each animal (Figure 2). Grids were placed in the same orientation and position relative to the snout and the dorsal midline on each animal to control for variation in skin thickness. On the left flank of each pig, 24 full-thickness wounds measuring 1.7 cm in diameter and 5 mm deep were created in each square using a punch biopsy technique (Figure 3A). On the right flank of each pig, 24 partial-thickness wounds of 2.0 × 2.0 cm were created in each square using a 1.6% croton oil–phenol peel (Figure 3B). The wounds were cleansed and dressed with transparent vapor-permeable film dressings and secured with elastic mesh stockings. The pigs were

Figure 2. A precisely cut grid was used to mark 24 squares (2.0 × 2.0 cm) on the left and right flanks of both pigs. The squares served as a template for wound creation.

Figure 3. Full- and partial-thickness wounds are shown on the control pig 7 days after surgery. (A) Full-thickness wounds produced by punch biopsy (1.7 cm diameter, 5 mm deep). (B) Partial-thickness wounds produced by chemical peel (2.0 × 2.0 cm).
then recovered from general anesthesia and housed in their cages.

Dressing changes were performed weekly or as needed for soiling, with the animals sedated by veterinary staff. The wounds were examined, photographed, and biopsied postoperatively on days 7, 14, and 28. Photographs of each wound were taken using a close-up lens with a millimeter ruler in the frame of each photo, to enable precise analysis of each wound. Wound area was evaluated by loading the standardized photo of each wound into MetaVue bioimaging software (Molecular Devices Corp, Sunnyvale, California). Using the software, each wound could be traced at its edges and the total area in number of pixels calculated (Figure 4). Using the scale in each photograph, the pixel area of each wound was converted to square centimeters.8,9

For histological analysis, 3.0-mm punch biopsies of 5 representative chemical peel wounds were taken on days 7 and 14. On days 14 and 28, biopsies of 5 representative full-thickness wounds were taken at the wound edges. Biopsies were taken from random locations but from corresponding wound locations on each pig. Specimens were fixed on slides and stained with hematoxylin and eosin (H&E). Histological analysis on all specimens was performed and interpreted by a dermatopathologist in a blinded fashion. On postoperative day 28, the pigs were euthanized by intravenous administration of pentobarbital 390 mg/mL (1 mL/5 kg).

Table 1. Comparison of the Mean Area of Full-Thickness Wounds in the Isotretinoin-Treated Animal and Control Animal at 2 and 4 Weeks Postoperatively

<table>
<thead>
<tr>
<th>Time Period, d</th>
<th>Control (n = 24) Mean Area, cm² ± SD</th>
<th>Isotretinoin Treated (n = 24) Mean Area, cm² ± SD</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.4346 ± 0.0816</td>
<td>0.4685 ± 0.1013</td>
<td>.21b</td>
</tr>
<tr>
<td>28</td>
<td>0.0689 ± 0.0866</td>
<td>0.0363 ± 0.0493</td>
<td>.12b</td>
</tr>
</tbody>
</table>

aTwo-sample (unpaired) t test.
bNo significant difference between the treated and control animals.

RESULTS

On subjective examination of the full-thickness wounds, there appeared to be no difference in wound size or character in the same areas of the respective flanks of each pig at 14 days (Figure 5A,B) and at 28 days (Figure 5C,D). At 28 days, total healing was observed in 12 full-thickness control wounds and 11 full-thickness experimental wounds. On quantitative analysis, the average full-thickness wound size in the control group at 14 days was 0.4346 cm² and 0.0689 cm² at 28 days. The average full-thickness wound size in the isotretinoin group at 14 days was 0.4685 cm² and 0.0363 cm² at 28 days. Mean wound sizes were compared at 14 and 28 days. Comparison via unpaired t test revealed no difference in wound size, with P values of .21 at 14 days and .12 at 28 days (Table 1). The 95% confidence interval (CI) for the difference of the mean of the control and experimental wounds was –0.095 to 0.028 cm² at 2 weeks and –0.080 to 0.015 cm² at 4 weeks. The mean wound area at each time point, with bars reflecting the 95% CI, is shown in Figure 6.

Due to variable amounts of eschar formation, the croton oil–phenol peel results were not statistically analyzed but were documented by photograph 14 days and 28 days after wound creation. Subjectively, the partial-thickness wounds of both pigs healed equally at 14 days (Figure 7A,B) and showed near complete healing at 28 days (Figure 7C,D). There was no evidence of aberrant scarring or pigmentation in either animal at 28 days.

On histological analysis 7 days after wound creation, the partial-thickness wounds of both pigs healed equally at 14 days (Figure 7A,B) and showed near complete healing at 28 days (Figure 7C,D). There was no evidence of aberrant scarring or pigmentation in either animal at 28 days.

On histological analysis 7 days after wound creation, the partial-thickness wounds on both the control and experimental pigs showed no significant differences. Both revealed scale crusting on the stratum corneum of the epidermis and mild fibrosis and reparative changes in the dermis (Figure 8A,B). Histological analysis at 14 days after wound creation revealed no significant abnormalities on either the control or the experimental pig. Both had a mild chronic inflammatory response in the superficial dermis along with mild fibrosis in the superficial or middle dermis (Figure 8C,D).
Histological analysis of the full-thickness wound specimens 14 days after wound creation showed erosion of the epidermal surface and development of granulation tissue in the superficial dermis of both the control and experimental pigs; however, the experimental pig had slightly more fibrosis admixed with the granulation tissue (Figure 9A,B). At 28 days, the control and experimental pigs showed similar histology, with a dense fibroblastic reaction involving the superficial and deep dermis (Figure 9C,D).

**DISCUSSION**

For years, conventional wisdom has held that it is necessary to delay invasive procedures for at least 6 months after treatment with isotretinoin to avoid poor or delayed wound healing. This recommendation is not supported by high levels of evidence, despite its wide acceptance. In fact, a recent literature review failed to show any conclusive relationship between retinoids and healing, and yet, in a recent, informal phone survey we conducted of over a dozen dermatologists and plastic surgeons in the vicinity of our medical college, we discovered that few, if any, would perform any invasive procedure or resurfacing on a patient who had been on isotretinoin within the past 6 months, and most would prefer to wait 12 months.

The first reports on isotretinoin and poor or delayed wound healing were 2 small case series reported in the 1980s. The first described 6 patients who had “recently” been on isotretinoin and experienced keloid formation following dermabrasion. This report was limited by its failure to detail outcomes on the remaining patients who had no recent history of isotretinoin and were treated in a similar fashion. The second report detailed 3 patients receiving isotretinoin treatment who developed keloids after dermabrasion or argon laser. One of these cases

![Figure 5. Full-thickness wounds on the control pig (A, C) and isotretinoin-treated pig (B, D). (A, B) Two weeks after the wounds were made. (C, D) Four weeks after the wounds were made.](image-url)
was a patient with a prior history of keloid scar formation. Neither study detailed the degree of skin pigmentation or ethnicity of the patients.

Subsequent reports have noted varied effects of retinoids on wound healing. There are multiple case series reporting normal healing in patients with recent isotretinoin use and laser treatment, dermabrasion, or surgery. Additional studies have attempted to reexamine the theory that retinoids adversely affect wound healing in the laboratory. These studies have involved administration of retinoids in several different animal models, including rats, guinea pigs, and rabbits. However, the drug was administered before the procedure only, after the procedure only, or both before and after the procedure in these studies. None of these mimic the clinical use of isotretinoin in humans. The resulting data are mixed and the articles lack specific recommendations.

The animal models previously used also raise the question of which animal skin most closely mimics human skin. The animals used in the studies to date differ from humans in hair distribution, dermal-to-epidermal ratio, and presence of a panniculus carnosus. Healing in animals such as rats, guinea pigs, and rabbits proceeds by a contraction mechanism, rather than by the epithelialization that is seen in humans. In contrast, pigs are known to have similar skin composition, hair patterns, and healing mechanisms as humans, making the pig the accepted animal model for human skin. The only previous retinoid

Figure 6. Mean wound area for experimental and control wounds, plotted versus time at 0, 14, and 28 days. Bars are drawn to show 95% confidence intervals at 14 days and at 28 days.

Figure 7. Partial-thickness wounds on the control pig (A, C) and isotretinoin-treated pig (B, D). (A, B) Two weeks after the wounds were made. (C, D) Four weeks after the wounds were made, both showing near-complete healing.
study performed on a pig model was done with topical administration, rather than systemic use.\textsuperscript{19} To parallel a clinical setting as closely as possible, we created 2 different types of wounds on each pig flank: 24 full-thickness wounds on the same flank of each pig and 24 superficial (partial-thickness) wounds on the opposite flank of each pig. The superficial wounds were created by application of a 1.6\% phenol–croton oil solution, as used clinically in a deep facial peel. This also simulated the skin damage that might be produced by a laser. All of the superficial wounds healed equally well, with no differences between the drug-treated and control pig. There was

Figure 8. Biopsy of partial-thickness wound number 4 on the control pig (A, C) and isotretinoin-treated pig (B, D). (A) The stratum corneum of the control pig shows focal orthokeratosis with scale crust 7 days after wound creation. In the dermis, there is a subtle superficial perivascular lymphocytic infiltrate with mild dermal fibrosis. (B) The stratum corneum of the isotretinoin-treated pig shows scale crust with parakeratosis 7 days after wound creation. In the dermis, there is a subtle proliferation of fibroblasts. (C) No abnormalities are seen in the biopsy from the control pig 14 days after wound creation. (D) The epidermis and dermis of the isotretinoin-treated pig show no diagnostic abnormalities 14 days after wound creation.
Figure 9. Biopsy of full-thickness wound number 4 on the control pig (A, C) and isotretinoin-treated pig (B, D). (A) The biopsy shows an eroded epidermis with granulation tissue in the dermis of the control pig 14 days after wound creation. (B) Granulation tissue is visible in the dermis with a subtle fibroblastic proliferation seen at the base in the isotretinoin-treated pig 14 days after wound creation. (C) Collagen bundles and the accompanying fibroblasts are characteristically oriented parallel to the skin surface in the biopsy of the control pig 28 days after wound creation. Capillaries are oriented perpendicular to the skin surface and are surrounded by a sparse inflammatory cell infiltrate. (D) Collagen bundles with many fibroblasts and perpendicularly oriented capillaries are seen in the biopsy of the isotretinoin-treated pig 28 days after wound creation.
also similar healing of the full-thickness wounds (all of which were able to be measured objectively) on both pigs, with no demonstration of compromised healing potential.

The strengths of this study include the use of an appropriate animal model with genetically related animals, a controlled study design, and precise wound size measurement using digital photographic analysis. This is also the first blinded histological investigation of the effects of isotretinoin on wound healing. Although the use of only 1 animal in each arm of the study is a limitation, fair statistical analysis was possible because there were a total of 96 wounds evaluated (24 on each flank of the 2 pigs). From a biostatistical standpoint, creating a larger number of wounds would result in only a small decrease in the detectable difference between control and experimental wounds. Another limitation of this study is the focus on acute healing, rather than long-term scar remodeling. Abnormal scar formation in an animal model, especially keloid formation, is very difficult to reproduce, which is why the current study focused only on the healing process. This work represents an initial step toward larger, controlled trials involving isotretinoin treatment in a porcine model, a model that we have found to be both feasible and humane. Future work by our group may include a larger number of study animals (although the 96 wounds created in the current study were sufficient to produce statistically significant data) and incorporation of other clinical scenarios, such as wounds closed with sutures. We believe that, when necessary, invasive procedures within 6 months of isotretinoin treatment may be safe and beneficial, as in the case of the 28-year-old patient described earlier in this report.

CONCLUSIONS

There appear to be no statistical or observational differences between the rates of wound healing in the isotretinoin-treated pig and control pig in this study. Although we do not yet suggest performing elective or aesthetic procedures at an earlier time, our findings suggest that invasive surgery might be safely performed in the presence of recent isotretinoin therapy earlier than the widely assumed time frame of 6 to 12 months. This finding challenges the current practice of waiting longer than 6 months after completing isotretinoin therapy to perform surgery and may benefit patients requiring more urgent surgical intervention.

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