Comparative trial of octyl-cyanoacrylate and silver sulfadiazine for the treatment of full-thickness skin wounds

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A prospective, randomized, blinded, controlled experimental trial was performed in pigs to compare the rates of reepithelialization of 126 full-thickness cutaneous 4-mm punches treated with an octyl-cyanoacrylate spray, silver sulfadiazine, or a dry gauze (controls). Full thickness biopsies were taken 7, 14, or 30 days later for histopathological evaluation of hematoxylin and eosin stained tissue sections by a dermatopathologist. The primary outcome measure was the proportion of wounds completely re-epithelialized at days 7 and 14. Secondary outcomes were the rates of infection, foreign body reactions, and the depth of any resulting cutaneous dells measured with a micrometer. Between-group comparisons were performed with ANOVA or Chi-square tests. Octyl-cyanoacrylate treated wounds re-epithelialized more slowly, as fewer wounds treated with octyl-cyanoacrylate were re-epithelialized at day 7 in comparison with silver sulfadiazine or control wounds (50% vs. 90% vs. 100%, $p < 0.001$). There were no infections or foreign body type reactions. Amounts of granulation tissue were similar among groups. Octyl-cyanoacrylate wounds were more depressed than silver sulfadiazine wounds at days 7 and 14 yet had similar histopathological characteristics at day 30. We conclude that treatment of small, full thickness cutaneous wounds with octyl-cyanoacrylate results in delayed re-epithelialization and dermal repair in comparison with silver sulfadiazine, yet it does not result in any foreign body–type reaction. However, by 30 days, histopathological wound characteristics were similar in all groups. **(WOUND REP REG 1999;7:356–361)**

Punch biopsies of the skin are routinely performed for diagnostic purposes. However, optimal management of the resulting wounds is unclear. Currently, most such wounds are treated with a topical antibiotic ointment and an adhesive dressing. A recent study by Smack et al. suggests that topical application of petrolatum ointment is a cost-effective alternative to topical antibiotics for the treatment of such wounds.[1]

Occlusive dressing therapy is an attractive alternative for the management of wounds resulting from punch biopsies. Prior studies in both animals and humans have clearly indicated that acute partial-thickness wounds re-epithelialize more rapidly under moist conditions provided by occlusive dressings.[2,3] Enhanced re-epithelialization of small full-thickness wounds under occlusive dressings has also been recently shown in pigs and humans.[4–6] Additional benefits of occlusive therapy include pain reduction and improved cosmetic outcome of wounds healed by both primary and secondary intention.[5,7,8]

OCA	Octyl-cyanoacrylate
SSD	Silver sulfadiazine

While tissue adhesives have been available outside the United States for many years,[9] their use has mostly been limited to surgical or traumatic wound closure and grafting.[10–17] On contact with a fluid medium the cyanoacrylates polymerize forming a strong solid film. While shorter chain cyanoacrylates were shown to result in inflammatory reactions, longer

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chain derivatives, such as butyl-and octyl-cyanoacrylate (OCA), have not been associated with significant toxicity.[18] We have recently shown that OCA (a new and improved tissue adhesive) significantly enhanced the re-epithelialization rate of deep partial thickness burns in swine compared to treatment with silver sulfadiazine (SSD) or dry gauze.[19] In addition to forming an occlusive coating over the wounds, the cyanoacrylates have also been shown to have both in vitro and in vivo antibacterial activity, particularly against gram positive organisms and may thus contribute to a reduction in wound infections.[20,21] OCA, available in a spray form, may easily be applied as a wound dressing conforming to surface contours and thus has the potential to be an ideal therapy for small wounds such as after punch biopsies. We are unaware of any prior studies evaluating the use of tissue adhesives as dressings for punch biopsy sites or other full-thickness wounds.

The objective of the current study was to compare wound healing of full-thickness wounds created by a 4-mm punch treated with OCA, SSD, and dry gauze in a porcine model.

METHODS

A randomized, controlled trial design was used to compare the re-epithelization and wound infection rates of full-thickness wounds created by punch biopsy treated with OCA spray, SSD, and dry gauze (controls). This project was approved by the institutional Animal Care and Use Research Review Board. Housing and care for animals was in accordance with the National Research Council guidelines.[22]

Animal Protocols

This study was conducted in the animal research laboratory of the Department of Emergency Medicine, State University of New York, Stony Brook, NY. Three pathogen-free female Yorkshire pigs weighing 20–30 kg were used. Domestic pigs were selected because of the morphological and functional similarities of pigskin with the human skin and the ability of the porcine model to predict wound healing in humans.[23] The animals were fed a basal diet ad libitum several days prior to experimentation and were housed individually.

All animals were sedated with Talazine® (Tiletamine and Zolazepam, Fort Dodge Lab, Fort Dodge, IA) 5 mg/kg IM. The pigs were then intubated endotracheally and maintained under a surgical plane of anesthesia with isoflurane 0.5–2.5% in room air.

The animals' backs and flanks were clipped with electric clippers and the skin scrubbed with a 7.5% povidine-iodine scrub and rinsed with normal saline. A 4-mm punch biopsy (Miltex Instrument Company, Inc., Lake Success, NY) was used to create full-thickness wounds over the paravertebral and flank areas of the pigs' skin using standard sterile surgical technique. All wounds extended into and included subcutaneous fat. Hemostasis was obtained by direct pressure with sterile gauze.

We performed three sets of experiments on three pigs. Each experiment was conducted on a separate pig. In all three experiments, one third of the wounds were randomly treated with OCA spray, one third were treated with SSD, and one third were treated with dry gauze (control). In the first experiment, 36 full-thickness wounds were made. The wounds were randomized to the three treatment groups as described and dressing changes were performed on days 1, 2, and 3 after injury. Full thickness 6-mm punch biopsies containing the original wounds were taken 7 days after injury for blinded histopathological evaluation by a board certified dermatopathologist. In the second experiment, 45 full-thickness wounds were similarly randomized to the three treatment groups and dressings were changed on days 1, 2, 3, and 7 after injury. Full thickness 6-mm punch biopsies containing the original wounds were taken 14 days after injury. In the final experiment, 45 full-thickness wounds were similarly randomized to the three treatment groups and dressings were changed on days 1, 2, 3, and 7 after injury. Full thickness 6-mm punch biopsies were taken 30 days later. After application of the assigned treatment, all wounds were covered with a nonadherent dressing (Telfa®, Kendall Company, Mansfield, MA). The pig was then wrapped with a gauze stretch bandage (Conform®, Kendall Company, Mansfield, MA) and an elastic adhesive bandage (Elastoplast®, Beiersdorf-Jobst, Inc., Rutherford College, NC). Dressings were kept in place by placing several staples at the edges of the adhesive dressing.

To limit the number of times that a general anesthetic would be administered to the pigs, we did not perform daily dressing changes as is customary. Prior studies suggest that most of the beneficial effects of moisture on healing occur within the first few days after injury.[24] Furthermore, most wound infections also occur within the first 3–4 days. Therefore we did not feel that limiting our dressing changes to the first 3–4 days would have had major impact on our results. Wound tissue was formalin fixed and embedded in paraffin. Sections were alcohol dehydrated,

xylene cleared, and stained with hematoxylin and eosin before examination by conventional microscopy.

Animals were observed daily for signs of pain or discomfort and treated with IM buprenorphine 0.01 mg/kg as needed.

Outcome Measures

The primary outcomes measured were the proportion of wounds completely re-epithelialized at days 7 and 14 after injury. Secondary outcomes measured were the percentage wound re-epithelialization at days 7 and 14, the rate of wound infections, the presence of foreign body reactions, and the depth of any cutaneous dells (cutaneous defects or depressions). Percent wound re-epithelialization was calculated by dividing the length of the re-epithelialized portions of the wounds by its total length. On a subset of 15 burns, this outcome had excellent interrater reliability (Pearson's correlation coefficient of 0.98, $p < 0.001$).[19] A wound was considered infected if interstitial dermal neutrophils containing intracellular bacteria were present.[21] The depth of any cutaneous dells was measured in μm using an ocular micrometer. This measurement was taken between a horizontal line connecting the epidermal basement membrane on either side of the wound and the deepest level of the dell. On a subset of 45 randomly chosen wounds in which the pathologist performed two separate measurements this outcome had excellent reliability (Pearson's correlation coefficient of 0.99, $p < 0.001$). At day 30 we also determined whether the level of the surface of wounds was flat, depressed or elevated in comparison with the surrounding normal skin on either side of the scar. All biopsies were evaluated for the presence of any inflammatory changes or foreign body reactions.

Data Analysis

Data were entered into Access 97 (Microsoft, Inc., Redmond, WA) and imported into SPSS 8.0 for Windows (SPSS, Inc., Chicago, IL) for statistical analysis. Continuous variables are presented as means with standard deviations; continuous variables that were not normally distributed are presented as medians and interquartile ranges. Categorical variables are presented as percentage occurrence and compared using Chi-square tests.

Skewness and kurtosis tests were performed to determine whether parametric or nonparametric tests could be used for between-group comparisons. One way analysis of variance (ANOVA) was used for comparison of normally distributed data (dell depth). Kruskall Wallis tests were used for comparison of non-normal data (percentage wound re-epithelialization).

Sample sizes were sufficient to detect an effect size of 0.6 in the primary outcome (proportion of wounds completely re-epithelialized) with a power of greater than 80% using a significance level of 0.05.[25]

RESULTS

We created 126 full-thickness wounds of which 36 were sampled after 7 days, 45 were sampled after 14 days, and 45 were sampled after 30 days. Seventeen wounds were excluded because the pigs had rubbed against them, partly removing the dressing, and abraded the area due to friction. Thus, in the 7-day experiment there were 10 wounds in the OCA group, 10 in the SSD group, and 8 in the control group. In the 14-day experiment there were 14 wounds in the OCA group, 13 in the SSD group, and 14 in the control group. In the 30-day experiment there were 13 wounds in the OCA group, 13 wounds in the SSD group, and 14 wounds in the control group.

There were significant between-group differences in the outcome measures at day 7 (Table 1). Fewer wounds treated with OCA were completely re-epithelialized than wounds treated with either SSD or controls (5/10 vs. 9/10 vs. 8/8, $p = 0.02$). The median percentage wound re-epithelialization for OCA wounds (85%) was significantly less than for wounds in the other two groups (100% in each, $p = 0.036$). Also, wounds treated with OCA were significantly more depressed than wounds treated with either SSD or dry gauze (1.9 mm vs. 0.6 mm vs. 0.8 mm, $p < 0.001$ [Table 1]).

At day 14, wounds treated with SSD were significantly less depressed than wounds treated with either OCA or dry gauze (170 μm vs. 412.4 μm vs. 337 μm, $p = 0.034$ [Table 2]). All wounds were completely re-epithelialized at day 14 after injury.

At day 30 there were no significant differences in the proportion of flat, depressed, or elevated wounds among the three treatment groups (Table 3). There were no wound infections or evidence of inflammatory or foreign body reactions noted in any of the wounds at any time. Similar amounts of granulation tissue were noted on wounds from all three groups.

DISCUSSION

The results of the current study indicate that in pigs, small full-thickness wounds resulting from a 4-mm

Table 1. Outcome measures seven days after injury.

Parameter	Treatment			*p*-value
	OCA	SSD	Controls	
n	10	10	8	
Re-epithelialized wounds, No (%)	5/10 (50%)	9/10 (90%)	8/8 (100%)	0.02
% re-epithelialization, median (IQR*)	85 (67–100)	100†	100†	0.036
Wound infections, No (%)	0 (0%)	0 (0%)	0 (0%)	NS
Dell depth, mean (SD), mm	1.9 (1.1)	0.6 (0.3)	0.8 (0.3)	< 0.001

*IQR = Inter Quartile Range

†All values = 100%

punch treated with OCA appeared to heal more slowly than wounds treated with either SSD or dry gauze. Fewer wounds in the OCA group were completely re-epithelilialized by day 7 and there was less granulation tissue present resulting in significantly deeper intradermal dells than in the other two groups. It is possible that the mechanical presence of an OCA plug, which completely filled in the defect resulting from the punch biopsy, resulted in a slower rate of re-epithelialization and delayed the rate at which the dermal defect granulated.

Early re-epithelialization was delayed in the OCA group, yet all wounds were completely re-epithelialized within two weeks. Early granulation tissue deposition was less in the OCA group, but by one month after injury there were no clinically or statistically significant between-group differences in the histopathological wound characteristics. Furthermore any differences noted at this time might have become even less apparent as the healing process proceeded. Thus the proportion of flat, depressed, or elevated wounds was similar among the groups. Furthermore, our study failed to show any increase in infection rates when OCA was used. We also did not find evidence of any foreign body reactions or infections in wounds treated with the tissue adhesive. Therefore, treatment of full-thickness wounds with OCA spray may retard wound re-epithelialization by several days and slow the rate of granulation tissue formation the dermal defect resulting from a punch biopsy. The mere presence of the tissue adhesive within the depths of the wound may also be holding the wounds open, which could result in retarded wound contraction. However, the delayed wound appearance after 30 days is similar to that resulting after treatment with either SSD or dry gauze.

The ability of occlusive therapy to speed epithelialization in both partial thickness and full-thickness wounds has clearly been shown. De Coninck et al. showed that 3×3 cm full thickness wounds in pigs covered with an occlusive dressing healed within 19 days while similar wounds covered with a nonocclusive dressing took 26 days to heal.[4] Similarly, Agren et al. has shown that full-thickness wounds resulting from a 20-mm punch re-epithelialized faster following occlusive therapy.[6] In a study of 174 patients on whom 226 shave and 3-mm punch skin biopsies were performed, Nemeth et al. reported faster healing and less pain in sites treated with an occlusive dressing.[5] As a result of the above studies, we hypothesized that wounds treated with an occlusive OCA spray might re-epithelialize faster than wounds treated with SSD or dry gauze. However, the beneficial effects of the occlusive nature of OCA were probably offset by the mechanical barrier created in the depth of the wounds, which led to delays in healing. In prior studies that evaluated occlusive dressings for full-thickness wounds the occlusive dressing did not fill the

Table 2. Day 14 outcome measures.

Parameter	Treatment			*p*-value
	OCA	SSD	Controls	
n	14	13	14	
Re-epithelialized wounds, No (%)	14/14 (100%)	13/13 (100%)	14/14 (100%)	NS
Wound infections, No (%)	0 (0%)	0(0%)	0(0%)	NS
Dell depth, mean (SD), μm	0.4 (0.5)	0.2 (0.1)	0.3 (0.4)	0.34

Table 3. Wound characteristics at 30 days after injury.*

Parameter	Treatment		
	OCA	SSD	Controls
n	13	13	14
Flat wounds, No (%)	3 (23.1)	1 (7.7)	4 (28.6)
Depressed wounds, No (%)	6 (46.2)	6 (46.2)	10 (71.4)
Elevated wounds, No. (%)	4 (30.8)	6 (46.2)	0 (0)

*No significant diferences were observed by χ^2 $p = 0.07$

entire gap remaining after wounding. This difference most likely explains the dissimilar results found in our study.

Our study is the first in which OCA was used for the treatment of small full-thickness wounds. OCA spray is an easy method for applying an occlusive dressing which readily conforms to all skin surfaces and contours. In addition to forming an occlusive, moisture-retaining environment, prior studies suggest that OCA has both in vitro and in vivo activity against gram positive bacteria. For example, Quinn et al. showed a reduction in infection rates when contaminated wounds were closed with OCA vs. standard sutures.[21] Thus, OCA may potentially reduce infection rates compared with other forms of therapy, however, in the current study there were no infections in any of the groups. It is unclear whether these potential advantages of treatment with OCA spray will offset the delay in re-epithelialization and filling of the dermal gap.

Prior studies have also indicated that cyanoacrylates may elicit a foreign body reaction when introduced directly into wounds.[26] As a result, recommendations to avoid allowing tissue adhesive to enter the depths of wounds have been made.[16] We did not see any evidence of such reactions in the current study. It is possible that any of these reactions may have resolved by day 7–14 at which point we histologically evaluated the wounds.

Our study has several limitations which merit further discussion. First, we only evaluated the short-term effects of the various treatments. Wound healing is a complex process, which continues for many months. Thus, we do not know whether there would be any between-group differences in the long term effects. Second, while the porcine model is used to simulate the human model, it is unclear whether our results would generalize to the clinical scenario. Third, our study used relatively small full-thickness wounds. It is unclear whether our results would differ using larger full-thickness wounds. Finally, our study did not include a standard occlusive dressing control group. Future studies should compare wound healing with OCA spray to other occlusive dressings.

In summary, we have shown delayed re-epithelialization of small full-thickness wounds treated with OCA in comparison with SSD and dry gauze. Use of OCA also resulted in deeper intradermal dells than in the other two groups. However, all wounds were completely re-epithelialized by day 14 and there were no differences in the scar characteristics by day 30. There were also no infections or foreign body reactions noted in with use of OCA. While use of OCA may be convenient, it may delay re-epithelialization of punch biopsies by several days.

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