

Nitric Oxide Advanced Healing Ointment Speeds Re-epithelialization in Excisional and Thermal Porcine Wound Models

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ABSTRACT

Novan is developing the Nitric Oxide Advanced Healing (NOAH) Ointment, which is based on the Company's Nitricil macromolecular technology, as a regenerative medicine approach based on the body's natural healing process.

In a porcine deep partial thickness burn model, three doses of NOAH Ointment were compared to placebo and a triple antibiotic ointment (n = 5 animals). Dressings were changed every other day and wounds were analyzed on Days 8, 11, and 14 for percent re-epithelialization by histology. Microscopic analysis indicated a clear trend toward faster re-epithelialization with the highest dose.

In a separate porcine partial thickness wound model (n = 8 animals), four doses of the NOAH ointment were compared to placebo, Tegaderm as an occlusive positive control, and air exposed wounds. Dressings were changed once daily. Results from the study indicate that the lower doses, 0.1% and 0.5%, demonstrated much faster rates of re-epithelialization. All 20 wounds in the lowest dose (0.1%) were completely healed by Day 6, two full days faster than any other group. Inflammatory cytokine assessments along with histological findings will also be presented.

These studies demonstrate the ability of topical nitric oxide to speed wound healing and illustrate the importance of evaluating the NOAH ointment dose and frequency of application in future clinical studies.

EXCISIONAL PORCINE WOUND MODEL

Study Protocol

Animals: 8 Yorkshire pigs, 30-45 kg

Wounding: Under general anesthesia, 160 deep partial thickness wounds (10mm x 7mm x 0.5mm deep) created on the back of each animal with an electrokeratome.

Treatment: Treatment applied and dressing changed once daily.

Biopsies: Collected daily between 4 and 11 days post-wounding.

Tissue Analysis: Epidermal migration assay.

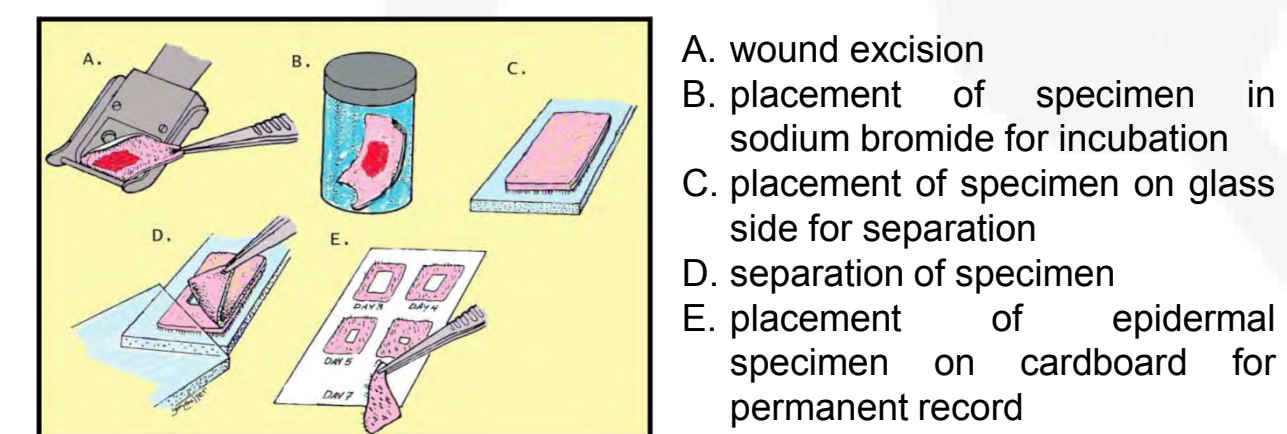


Figure 1. Example Excisional Porcine Wound Study Layout. Ointments containing 0.1% and 0.5% were evaluated in separate studies.

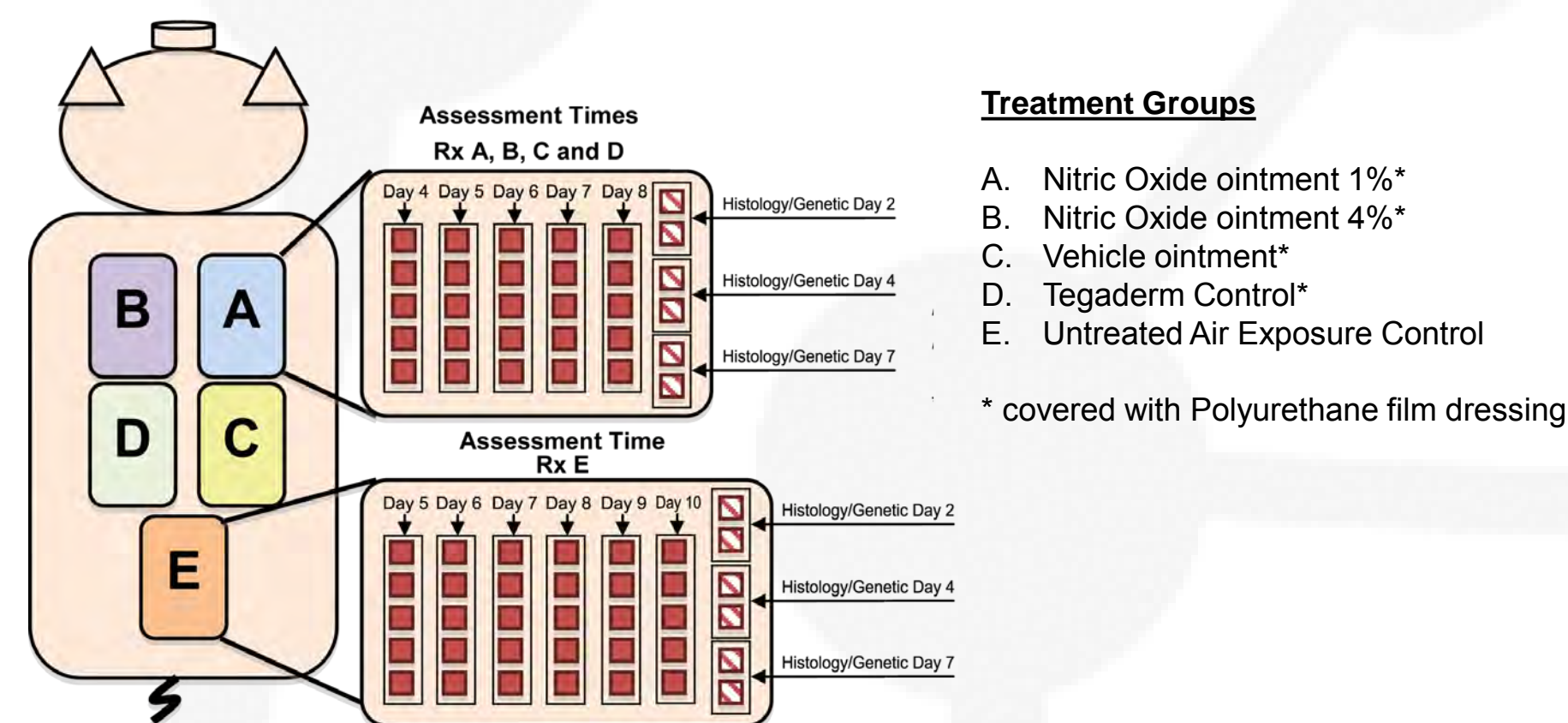
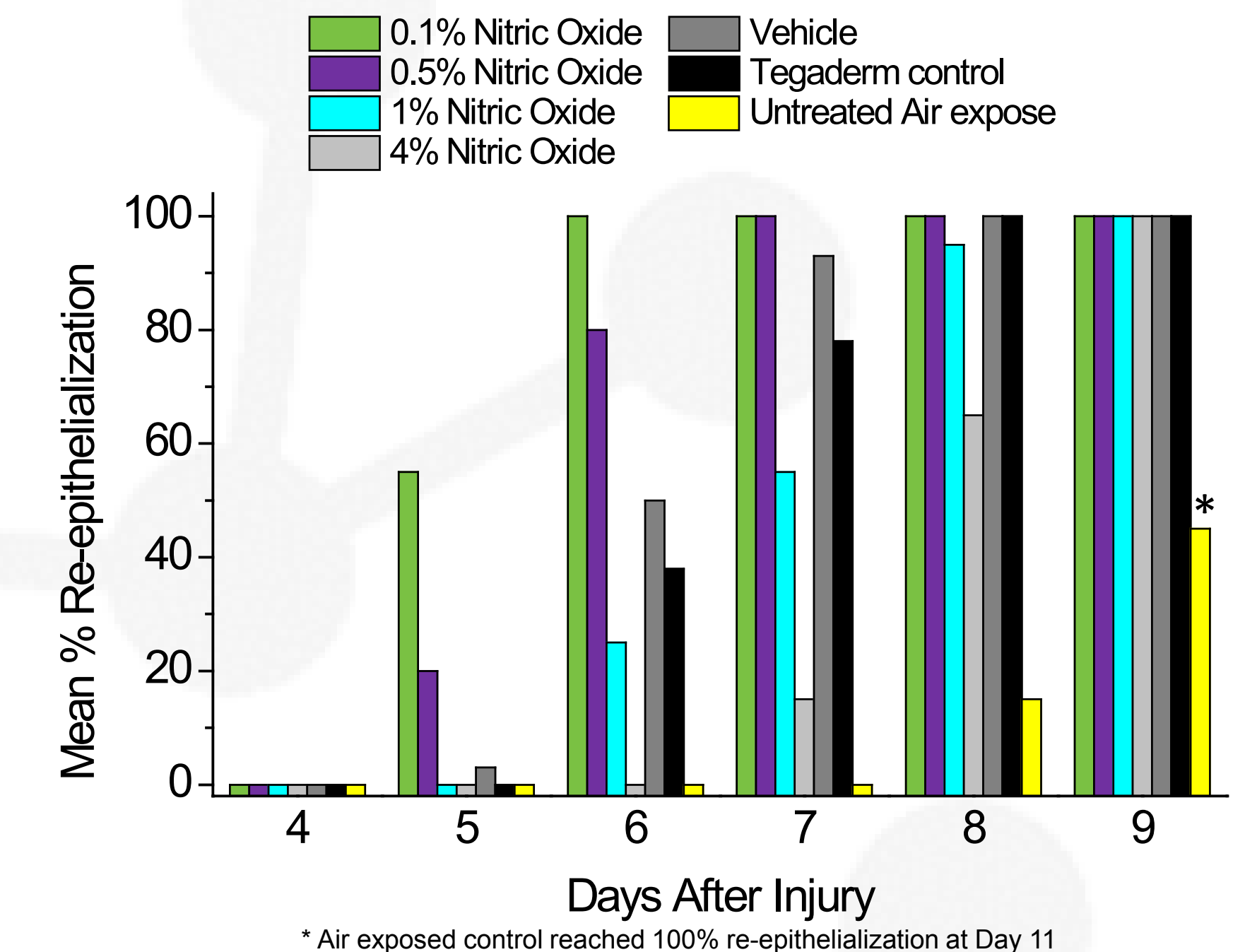


Figure 2. Mean % Re-epithelialization Following Excisional Wounding and Treatment.



THERMAL PORCINE WOUND MODEL

Study Protocol

Animals: 5 Yorkshire pigs, 20-25 kg

Wounding: Under general anesthesia, 20 burns (2.5cm x 2.5cm) created on the back of each animal by applying 80 °C aluminum bar for 20 seconds. Necrotic epidermis gently scraped away.

Treatment: After initial treatment, wounds dressed with gauze and a bandage. Reapplication of treatment and dressing were performed at 2, 4, 7, 9, 11, 16, 18, 21, 23, and 25 days after wounding.

Biopsies: Collected on 8, 11, and 14 days post-wounding.

Tissue Analysis: Microscopic tissue histology.

Figure 3. Thermal Porcine Wound Study Layout.

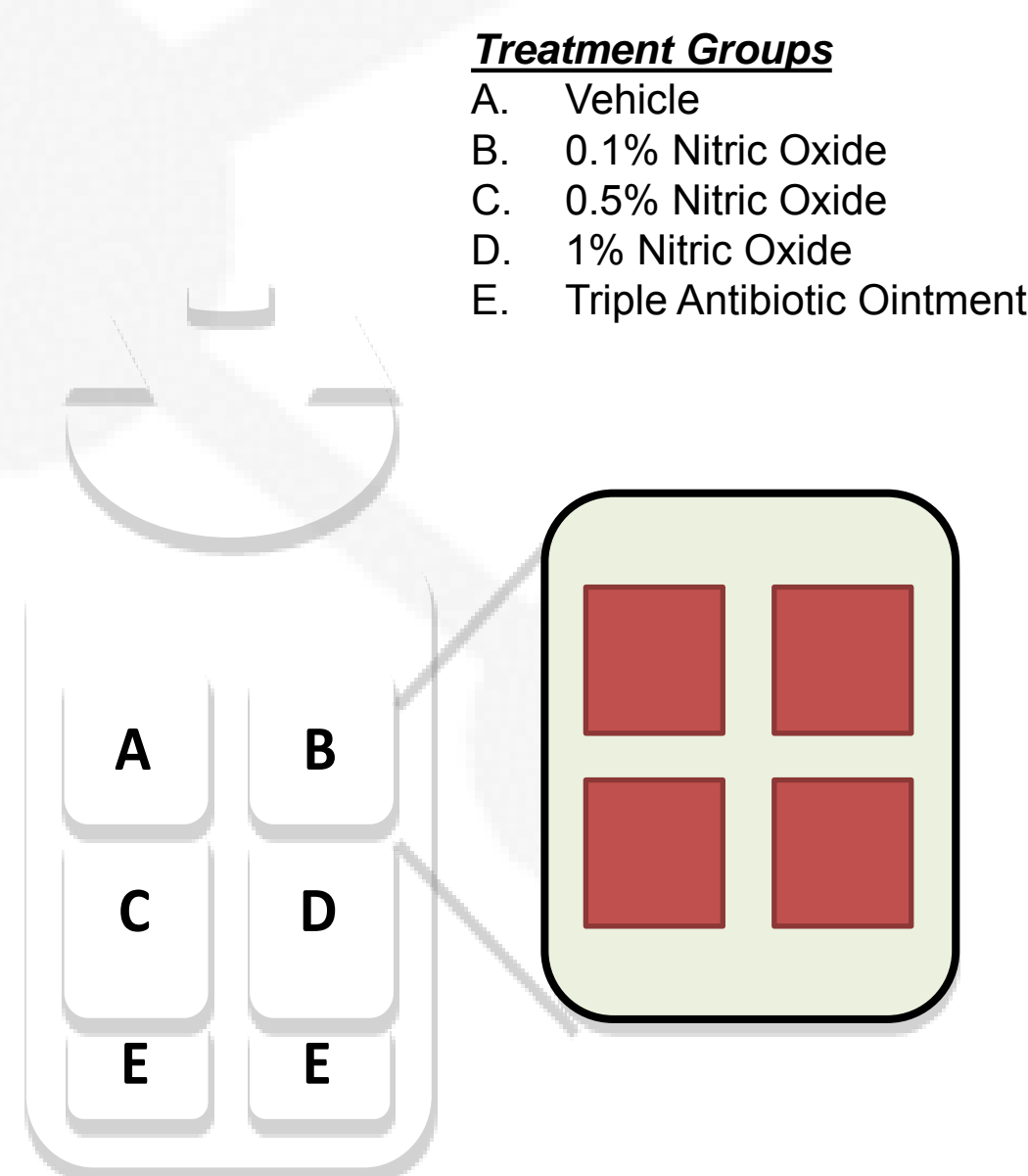


Figure 4. Appearance of Burn Wounds Immediately Following, 4 Days, and 8 Days Post-wounding.

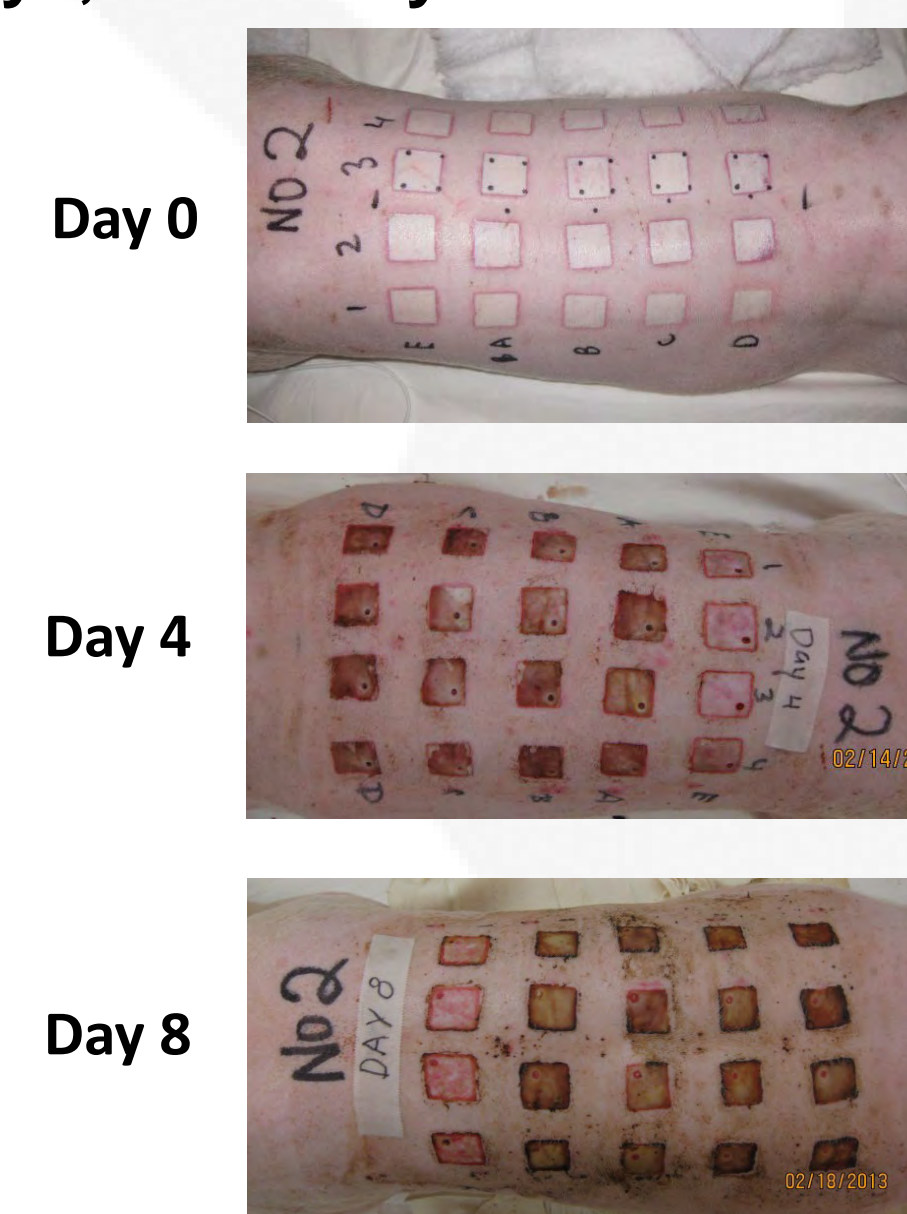
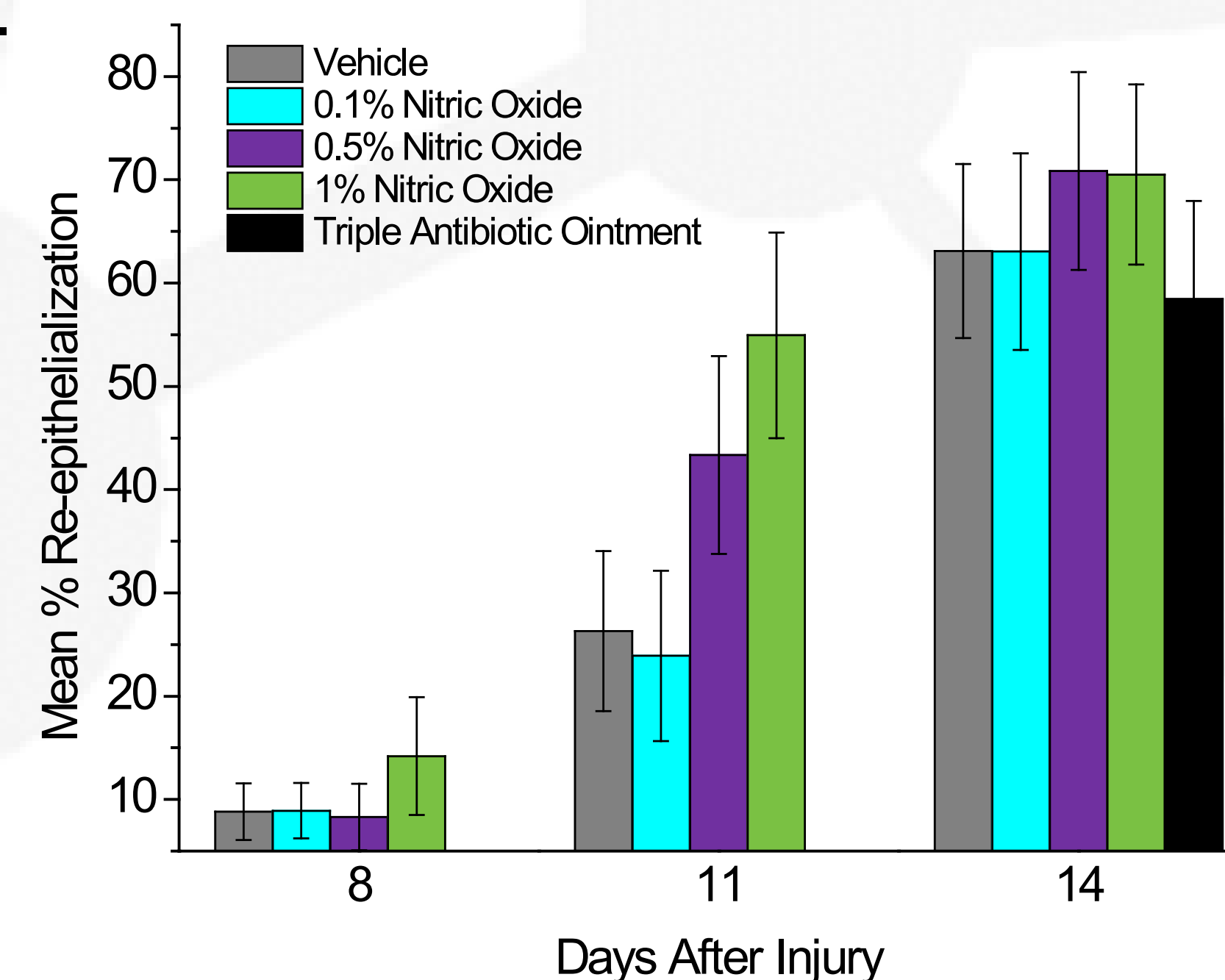


Figure 5. Mean % Re-epithelialization Following Thermal Wounding and Treatment.



- In the excisional porcine wound model, lower dose ointments (0.1% and 0.5% nitric oxide) demonstrated faster rates of re-epithelialization than high doses or controls. All wounds in the low dose group were healed by day 6, two full days faster than any other group. Expression of IL-8, a neutrophil chemo attractant, was significantly induced in wounds following 2 days of treatment with the 0.5% dose ($p \leq 0.05$). White cell infiltrate was not statistically different among any of the treatment groups.
- In the thermal porcine wound model, microscopic analysis indicated that application of 0.5% and 1% nitric oxide ointments increased the speed of re-epithelialization vs. 0.1% nitric oxide and vehicle.
- Together, these studies demonstrate the ability of topical nitric oxide to speed wound healing in multiple wound types and illustrate the importance of evaluating the NOAH ointment dose and frequency of application in future clinical studies.

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