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The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel☆

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Summary Hypertrophic scars can be reduced by the application of silicone dressing; however, the detailed mechanism of silicone action is still unknown. It is known that silicone gel sheets cause a hydration of the epidermal layer of the skin. An in vitro co-culture experiment has shown that hydration of keratinocytes has a suppressive effect on the metabolism of the underlying fibroblasts resulting in reduced collagen deposition.

We tested the hypothesis that silicone sheeting in vivo has a beneficial effect on scarring by reducing keratinocyte stimulation, with a resulting decrease in dermal thickness, hence scar hypertrophy.

Silicone adhesive gel sheets were applied to scars in our rabbit ear model of hypertrophic scarring 14 days postwounding for a total of 16 days. Scarring was measured in this model by the scar elevation index (SEI), a ratio of the area of newly formed dermis to the area of the dermis of unwounded skin, and the epidermal thickness index (ETI), a ratio of the averaged epidermal height of the scar to the epidermal thickness of normal epidermis. Specific staining [anti-PCNA (proliferating cell nuclear antigen) and Masson trichrome] was performed to reveal differences in scar morphology.

SEIs were significantly reduced after silicone gel sheet application versus untreated scars corresponding to a 70% reduction in scar hypertrophy. Total occlusion reduced scar hypertrophy by 80% compared to semi-occlusion. ETIs of untreated scars were increased by more than 100% compared to uninjured skin. Silicone gel treatment significantly reduced epidermal thickness by more than 30%.

Our findings demonstrate that 2 weeks of silicone gel application at a very early onset of scarring reduces dermal and epidermal thickness which appears to be due to a reduction in

☆ These results have partly been presented at the 15th Annual Meeting of the Wound Healing Society in Chicago, Illinois, USA, 2005.

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keratinocyte stimulation. Oxygen can be ruled out as a mechanism of action of silicone occlusive treatment. Hydration of the keratinocytes seems to be the key stimulus.
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Normal cutaneous wound healing is a finely controlled dynamic event involving the overlapping stages of inflammation, cell proliferation and matrix deposition. The latter is followed by gradual resolution involving collagen reorganisation and loss of cellularity. Over a period of up to 2 years a cutaneous wound usually resolves to a flat supple scar without functional consequences.[1,2]

In some cases the scar as an inevitable response to injury leaves a restriction of motion, and visible disfigurement due to abnormal scar formation. Scar hypertrophy appears when normal control mechanisms fail resulting in increased dermal cellularity and collagen deposition.[3–5]

Hypertrophic cutaneous scarring has classically been viewed as a dermal process. The up-regulation of collagen synthesis and deposition as well as decreased collagen degradation result in collagen accumulation, hence scar hypertrophy.[2,6] Therefore investigational strategies to reduce scarring have been focused on inhibiting collagen deposition, directly by impeding synthesis or indirectly by blocking transforming growth factor beta (TGF-beta) pathways.[7–11]

However, another line of evidence has implicated the epidermis as an important factor. Clinically, burn injuries and other superficial injuries, in which epithelialisation is delayed, result in hypertrophic scarring.[12] Epidermal-dermal interactions seem to regulate scarring as in vitro experiments have revealed.[13–17]

Multiple treatments have been tried, and most have been empirical.[18,19] Aside from local corticosteroid injections, silicone gel sheeting has been observed clinically to be effective since it was first reported in the 1980s and demonstrated in prospective randomised trials by Ahn and Mustoe[20,21] with the patient serving as their own control. Many other studies have been realised since and bolstered these findings, but the mechanism of action of silicone has not been identified so far. Pressure, temperature, oxygen tension or chemical properties of silicone were ruled out as a mode of action.[22,23]

There is some evidence that increased hydration of the stratum corneum is the potential cause of silicone's beneficial effect on hypertrophic scars.[24,25] Nevertheless, the permeability of silicone gel to oxygen in contrast to other semi-occlusive dressings has been one potential important mechanistic explanation.

The scarring process has been difficult to study because of the relative absence of excessive cutaneous scarring in animals, and the lack of applicability of in vitro systems. The availability of our rabbit hypertrophic scar model opened up the possibility of investigating silicone action in vivo more closely.[26,27]

The aim of this study was to investigate in an in vivo setting the importance of timing and intensity of occlusion, the role of oxygen as a mechanism of action in occlusion and finally the epidermal thickness in hypertrophic scarring.

Material and methods

Hypertrophic scar model

Six young adult New Zealand White female rabbits weighing between 2.5 and 3.5 kg were used in this study. The animals were handled according to procedures approved by the Northwestern University Animal Care and Use Committee. After the animals were anaesthetised with ketamine (60 mg/kg) and xylazine (5 mg/kg) we followed our standardised protocol for the hypertrophic scar as previously described.[8,26,27] Briefly, four wounds were created down to bare cartilage on the ventral surface of each ear by means of a 7-mm punch biopsy at standardised locations. A dissecting microscope was used to ensure removal of the epidermis, dermis and perichondrium in each wound. Removal of the perichondrial layer delayed epithelialisation of the 7-mm defect, which supports hypertrophic scar formation. Haemostasis was then obtained by applying pressure and each wound was individually covered with polyurethane dressing (Tegaderm®; 3M Health Care, St Paul, MN, USA).

Semi-occlusion and total occlusion

For treatment the rabbits had four wounds on each ear. The wounds were kept covered with polyurethane dressing until day 14 postwounding until the entire wound appeared re-epithelialised. Almost all wounds were re-epithelialised by day 12, and 50% were re-epithelialised by day 7.

In three rabbits semi-occlusive treatment with adhesive silicone gel sheets (CicaCare®; Smith & Nephew, Largo, FL, USA) was started on day 14 postwounding and then maintained for a total of 16 days until day 30 postwounding. The control wounds of the contralateral ear remained uncovered.

In the remaining three rabbits a comparison between semi-occlusion and total occlusion took place. Complete occlusion to water and oxygen was achieved by covering the wounds with silicone gel sheets and an additional four layers of polyurethane dressing (Tegaderm®; 3 M Health Care, St Paul, MN, USA). The wounds of the control ear were covered with silicone gel sheets only.

The water vapour transmission rates of silicone gel (CicaCare® $5.2 \pm 0.5\ g/m^2/hr$), and polyurethane film (Tegaderm®, $27.0 \pm 0.5\ g/m^2/hr$), were measured by means of the international ASTM E96-95 Desiccant Method as described previously.[28,29]

Gilman found that polyurethane film reduces oxygen permeability of a silicone gel sheet by a factor of 10.[30] In a personal communication with the author we elaborated the experimental set-up of the experiments presented here. Relying on his data we stated that an additional

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