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Research Article

Effects of Silicone-Based Gels Containing Allantoin, Dexpanthenol and Heparin on Hypertrophic Scarring in the Rabbit Ear Model

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ABSTRACT Silicone-based formulations are extensively used for the management of hypertrophic scars. Although the exact mechanism of action is still unknown, it has been postulated that some occlusion and hydration of the stratum corneum with subsequent cytokine-mediated signaling from keratinocytes to dermal fibroblasts is involved in its antiscarring effects. In this study, the effectiveness of silicone-based gels containing allantoin, dexpanthenol, and heparin was evaluated for improving the healing of hypertrophic scars. It was found that silicone-based gels showed remarkable improvements in hypertrophic scar healing and low amounts of skin pigmentation in the rabbit ear model compared with the nontreated control or base alone. Furthermore, the histopathological and histomorphometrical profiles of three different formulations containing 1%, 5%, and 20% silicone contents exhibited marked or significant decreases in the scar elevation index, anterior skin and epithelial thicknesses, inflammatory cells, vessels, collagen disorganization, and fibroblasts compared with nontreated control hypertrophic scars. Therefore, these results indicate that silicone-based gels containing heparin, allantoin, and dexpanthenol could be promising formulations for the healing of hypertrophic scars. Drug Dev Res 73 : 146–153, 2012.

Key words: silicone; hypertrophic scar; gel; heparin; allantoin; dexpanthenol

INTRODUCTION

Hypertrophic scars are a major clinical problem, yet few therapeutics are available to prevent or treat scar formation [Gallant-Behm and Mustoe, 2010]. The healing process can be related to inflammation leading to epithelization, the formation of granulation tissue, and tissue remodeling [Evans, 1980]. Wound healing involves overlapping steps of inflammation, cell migration and proliferation, neovascularization, extracellular

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matrix production, and remodeling, and collagen is major component of the extracellular matrix [Froget et al., 2003]. Inflammation followed by tissue repair is a complex physiological process aimed at the restoration of normal functioning after infection or wounding [Singer and Clark, 1999]. Hypertrophic scarring typically occurs as a result of a full thickness injury to the dermis with an abnormal healing response [Saulis et al., 2002a]. Numerous factors are involved in this hypertrophic scarring, including keratocytes, various cytokines and related inflammations, neovascularization, and fibrosis [van der Veer et al., 2009]. Hypertrophic scars can cause sensations of itchiness and pain, and erythema and pigmentation. In addition, they can potentially develop several complications such as secondary infections and skin tensions with cosmetic disfigurement [Brissett and Sherris, 2001; Tsao et al., 2002].

Various therapeutic methods including surgical excision, silicone gel dressings, topical treatments, intralesional corticosteroids, cryotherapy, radiation, compression therapy, and laser therapy have been tried to improve symptoms and induce regression in hypertrophic scars [Beuth et al., 2006]. Among these multiple treatments, topical silicone-based products have become established as first-line therapies for hypertrophic scarring due to their superiority in the prevention of the development of abnormal scarring [Saulis et al., 2002a]. In particular, silicone gels have advantages owing to their ease of use and improvements in patient compliance.

Therefore, self-drying, topical silicone-based gels containing dexpanthenol, allantoin, and heparin as active ingredients were developed for the prevention and treatment of hypertrophic scars. Dexpanthenol, the stable alcohol analog of pantothenic acid, can hasten healing of the epidermis and allantoin acts as a keratolytic agent that softens keratin found in the epidermis. In addition, the interaction of heparin with collagen molecules facilitates wound healing.

In this study, the efficacy of formulations containing allantoin, dexpanthenol, and heparin, with varying silicone contents of 1%, 5%, and 20% (designated as Noscarna 1%, Noscarna 5%, and Noscarna 20%, respectively), was evaluated for improvements in the healing of hypertrophic scars in the rabbit ear model. These formulations were compared with a control (natural healing), a base control (without the active agents), and a commercial product (Contractubex, Merz Pharm., Frankfurt, Germany). A unique hypertrophic scarring model in the rabbit ear was created by removing the perichondrium, thereby creating wounds down to the bare cartilage. Changes in color were monitored, and a histological analysis was performed to determine whether or not these products had an effect on scar hypertrophy.

MATERIALS AND METHODS

Materials

Silicone-based gels containing allantoin, dexpanthenol, and heparin with different silicone contents (Noscarna 1%, Noscarna 5%, and Noscarna 20%) were obtained from Dong-A Pharmaceutical Co. Ltd (Yongin, South Korea). One gram of each Noscarna formulations contains a fixed amount of 50 mg allantoin, 100 mg dexpanthenol, 500 IU heparin as active ingredients, along with varying silicone oil contents of 1%, 5%, and 20%, and 20% glycerin in distilled water. Contractubex gel (Merz Pharm.) containing 100 mg extractum cepae, 50 IU heparin, and 10 mg allantoin per one gram was commercial product. All of the other chemicals were of reagent grade and were used without further purification.

The Hypertrophic Scar Model

A rabbit ear model for hypertrophic scarring was used to compare the efficacy of silicone-based gels (Noscarna 1%, Noscarna 5% and Noscarna 20%) and a commercial product (Contractubex). Hypertrophic scars were created in rabbit ears as previously described [Morris et al., 1997; Marcus et al., 2000; Saulis et al., 2002a,b]. Briefly, 12 young adult New Zealand White female rabbits weighing between 2.5 and 3.5 kg (Samtaco, Osan, South Korea) were used in this study. The rabbits were anesthetized with Zoletil (15 mg/kg; Virbac S.A., Carros, France) and xylazine (5 mg/kg), and two wounds were created down to bare cartilage on the ventral surface of each ear by means of an 8-mm dermal biopsy punch (Miltex, Inc., York, PA, USA) at standardized locations. The removal of the epidermis, dermis, and perichondrium in each wound was checked using a dissecting microscope. Hemostasis was then achieved in all of these animals by applying pressure, and all wounds were covered using an occlusive polyurethane dressing (Tegaderm; 3M Health Care, St Paul, MN, USA). Handling of all animals and the experimental procedures were approved by the Yeungnam University Animal Care and Use Committee.

Treatment

Two wounds on each rabbit ear were available for treatment. Polyurethane dressing was used to cover the wounds until day 12 postwounding, until the entire wound appeared to be reepithelialized. Treatment with

different formulations of silicone-based gels was started on day 28 postwounding. The materials tested in this study included a base control without active ingredients, three silicone-based gel formulations (Noscarna 1%, Noscarna 5%, and Noscarna 20%) and Contractubex. The rabbits were treated three times a day with the abovementioned materials from day 28 until day 56, for total of 4 weeks. Six wounds were each treated with Noscarna 1%, Noscarna 5%, and Noscarna 20%, and Contractubex, the base control, and six wounds were left uncovered to serve as nontreated controls.

Color Analysis

Color measurements of the scars on the ears of the rabbits were undertaken using a spectrophotometer CM-3500d (Minolta Co., Ltd. Osaka, Japan). The color difference was measured before treatment and at 1 and 4 weeks after treatment using SpectraMagic_NX software (Konica Minolta). All values were normalized as a percentage of change from the baseline color expression.

Histological Process

On day 56 postwounding, all the rabbits were sacrificed and the scars were harvested. The scars were bisected in the centre at the height of the hypertrophic scar with a 0.5-cm rim of normal unscarred tissue around the scar to include ear cartilage as described in previous methods [Marcus et al., 2000; Saulis et al., 2002b]. All trimmed scars were fixed in 10% neutral-buffered formalin and embedded in paraffin. After embedding in paraffin, 3–4 μm sections were prepared. Representative sections were stained with hematoxylin and eosin for light microscopy examination and Masson's trichrome staining for collagen fiber visualization [Sung et al., 2010]. After this, the histological profiles of individual skin samples were observed under a light microscope (Nikkon E400, Kawasaki, Japan).

Histomorphometry

The scar elevation index (SEI) was employed for the histomorphometric analysis as described in previous methods [Morris et al., 1997; Marcus et al., 2000]. The SEI measures the ratio of total scar area connective tissue height to the area of the underlying dermis. The height of the underlying dermis was determined based on the height of the adjacent unwounded dermis. All measurements were taken within the confines of the wounded area, and the epithelial height was not considered in the SEI calculations. An SEI value equal to 1 indicates that the wound healed essentially flat, with no scar hypertrophy, 1.5 indicates that the scar thickness or hypertrophy was 50% of the normal unscarred dermal thickness, and 2 indicates a wound that healed with a 100% increase in normal tissue dermal thickness [Saulis et al., 2002a]. The anterior skin thickness from the epidermis to the dermis of the scar was calculated using a digital image analyzer (DMI-300, DMI, Seoul, South Korea) under ×50 magnification by a light microscope [Cho et al., 2008]. The numbers of infiltrated inflammatory cells (cells/mm^2 of scar), fibroblasts, and granulation vessels (vessels/mm^2 of scar) were also measured on cross-trimmed individual scar tissue samples using a digital image analyzer. In addition, collagen organization was further examined in a semi-quantitative manner [Saulis et al., 2002a]. This semi-quantitative assessment was composed of a visual rating under a light microscope, on a scale of 1 to 4, of the dermal areas of each hypertrophic scar on each Masson's trichrome-stained slide, with higher values indicating more disorganized collagen. Six scars in each group were considered as analysis.

Statistical Analysis

Multiple comparison tests were conducted for different dose groups. Variance in homogeneity was examined using the Levene test [Levene, 1981]. If the Levene test result showed no significant deviations from variance homogeneity, the data obtain were analyzed by one-way analysis of variance followed by a least significant differences multicomparison test to determine which pairs of group comparisons were significantly different. However, if the Levene test showed significant deviations from variance homogeneity then a nonparametric comparison test, the Kruskal–Wallis *H* test, was conducted. When a significant difference was observed in the Kruskal–Wallis *H* test, the Mann–Whitney U test was used to determine the specific pairs of the group comparison that were significantly different. Statistical analyses were conducted using SPSS for Windows (Release 14.0K, SPSS Inc., Chicago, IL) [Ludbrook, 1997]. In order to observe detailed effects of the base, the changes between the base control and the control were calculated, and also the changes between the base control and the test material-treated groups were calculated to help understand the efficacy of the test materials, as follows:

$$\text{Percentage changes compared with control (\%)} = ([\text{base control data} - \text{control data}]/\text{control data}) \times 100$$

$$\text{Percentage changes compared with base control (\%)} = ([\text{tested group data} - \text{base control data}]/\text{base control data}) \times 100$$

RESULTS

Color Analysis of the Scars

The color analysis of the scars showed that skin pigmentation on the hypertrophic scars treated with the three different formulations of Noscarna from postwounding day 28 to postwounding day 56 (4 weeks) was significantly reduced compared with the nontreated and base controls (Fig. 1). Notably, Noscarna 20% showed a greater decrease in pigmentation compared with Noscarna 1%, Noscarna 5%, and Contractubex after postwounding days 56. This result indicates that silicone-based gel formulations containing allantoin, dexpanthenol, and heparin have remarkable effects on reducing the skin pigmentation caused during hypertrophic scarring, particularly since the skin pigmentation was almost reduced to normal skin coloration by the formulation with the highest silicone content. The representative images of hypertrophic scars before and after 4 weeks of treatment in the rabbit ear model were displayed in Figure 2.

SEI

The hypertrophic scars treated with all three silicone-based gel formulations (Noscarna 1%, Noscarna 5, and Noscarna 20%) and Contractubex showed a significant decrease in the SEI compared with the nontreated wounds kept as controls and the base control scars (Fig. 3). The SEIs of Noscarna 1%, Noscarna 5%, and Contractubex were almost same. However, although not statistically significant, Noscarna 20% showed a lower SEI value compared with Noscarna 1%, Noscarna 5%, and Contractubex. This result indicates that all three formulations of Noscarna were able to reduce the SEI. Therefore, we can say that Noscarna has potent inhibitory effects on hypertrophic scarring and its efficacy was increased by the silicone-based formulation used in this study.

Histological Analysis

All three formulations of Noscarna were able to reduce anterior skin thickness, epithelial thickness, collagen disorganization, and the number of infiltrated inflammatory cells, vessels, and fibroblasts compared with the nontreated control and the base control (Fig. 4 and Table 1). The values obtained for Noscarna 1% and Noscarna 5% were very close and they were also close to Contractubex, whereas Noscarna 20% showed much lower values compared with Noscarna 1%, Noscarna 5%, and Contractubex. However, there was no statistically significant difference between Noscarna formulations.

DISCUSSION

Hypertrophic scars and keloids commonly occur as a result of postsurgical, thermal, and traumatic injuries to the skin. Characteristics of these lesions are an increased density of fibroblasts and overabundant

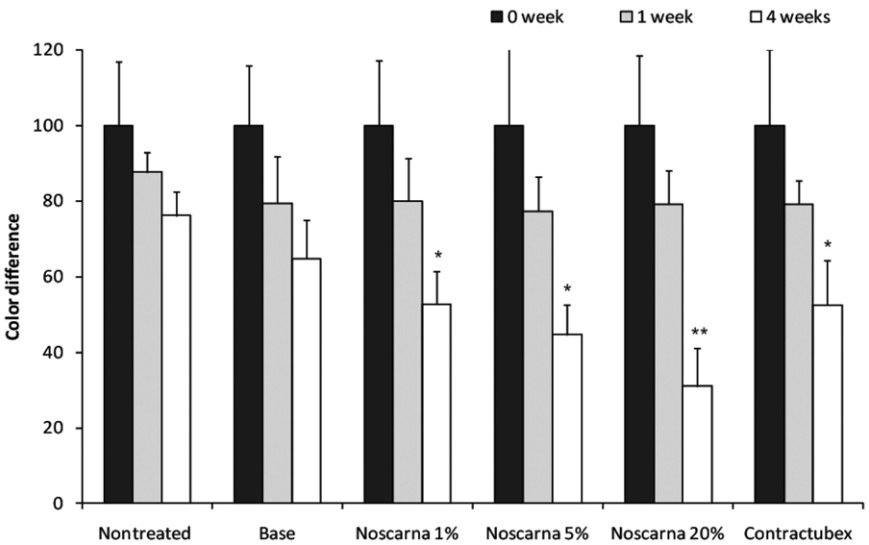

Fig. 1. Changes in skin pigmentation on the hypertrophic scars treated with the three different formulations of Noscarna from postwounding day 28 (0 week) to postwounding day 56 (4 weeks) in the rabbit ear model. Values are expressed as mean ± SD of six scars and normalized as a percentage of change from the baseline color expression. *$P < 0.05$ compared with the base control and nontreated control by the LSD test. **$P < 0.01$ compared with the base control and nontreated control by the LSD test.

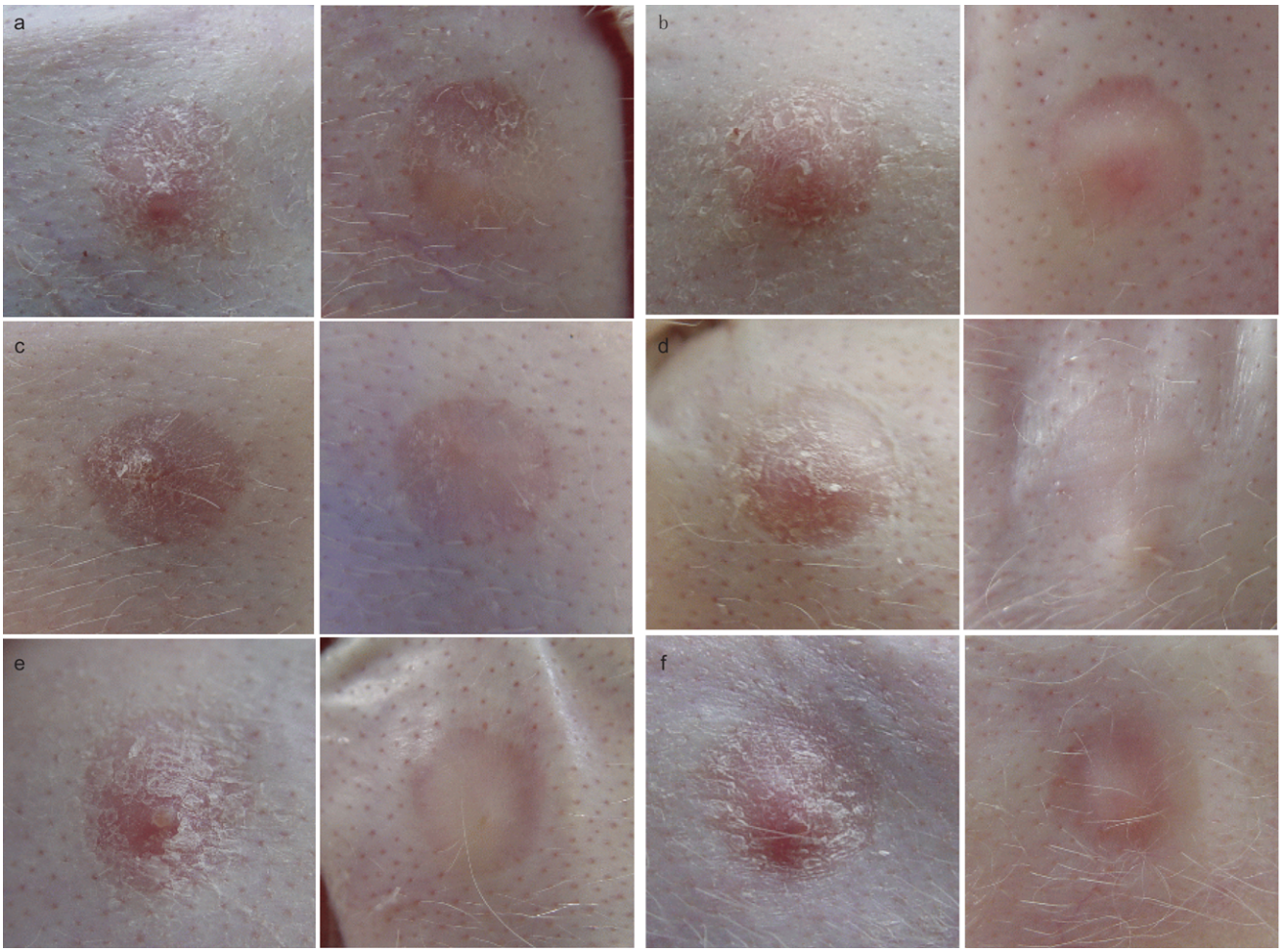

Fig. 2. The representative images of hypertrophic scars before and after 4 weeks of treatment in the rabbit ear model. (a) Nontreated control, (c) base control, (e) Noscarna 1%, (b) Noscarna 5%, (d) Noscarna 20%, and (f) Contractubex. [Color figure can be viewed in the online issue which is available at wileyonlinelibrary.com]

TABLE 1. Histomorphometrical Changes in This Study

	Controls		Commercial	Noscarna		
Groups histomorphometry	Nontreated	Base	Contractubex	1%	5%	20%
Anterior skin thicknesses (mm)	1.50 ± 0.16	1.01 ± 0.09[a]	0.72 ± 0.14[ac]	0.71 ± 0.06[ac]	0.73 ± 0.10[ac]	0.62 ± 0.08[ac]
Epithelial thicknesses (μm)	141.20 ± 18.39	100.13 ± 24.08[e]	70.84 ± 13.93[eg]	74.78 ± 8.27[eg]	73.09 ± 8.79[eg]	61.04 ± 9.17[ef]
Inflammatory cells (cells/mm^2 of scar)	36.67 ± 10.93	22.67 ± 3.98[e]	12.33 ± 4.46[ef]	12.00 ± 2.37[ef]	11.83 ± 3.97[ef]	5.83 ± 1.47[ef]
Vessels (numbers/mm^2 of scar)	39.17 ± 5.49	30.17 ± 3.82[a]	20.50 ± 6.44[ac]	20.17 ± 6.05[ac]	20.33 ± 7.42[ac]	13.33 ± 4.41[ac]
Collagen organizations (score)	3.50 ± 0.55	2.67 ± 0.52	1.83 ± 0.75[a]	1.83 ± 0.75[a]	1.67 ± 0.82[ad]	1.33 ± 1.03[ac]
Fibroblasts (cells/mm^2 of scar)	353.67 ± 83.42	224.67 ± 49.16[e]	138.00 ± 47.18[eg]	135.17 ± 32.85[ef]	138.17 ± 46.67[eg]	92.00 ± 20.82[ef]

Values are expressed as mean ± standard deviation of six scars.
[a]$P < 0.01$and [b]$P < 0.05$ compared with the nontreated control by the least significant difference (LSD) test.
[c]$P < 0.01$ and [d]$P < 0.05$ compared with the base control by the LSD test.
[e]$P < 0.01$ compared with the nontreated control by the Mann–Whitney (MW) test.
[f]$P < 0.01$ and [g]$P < 0.05$ compared with the base control by the MW test.

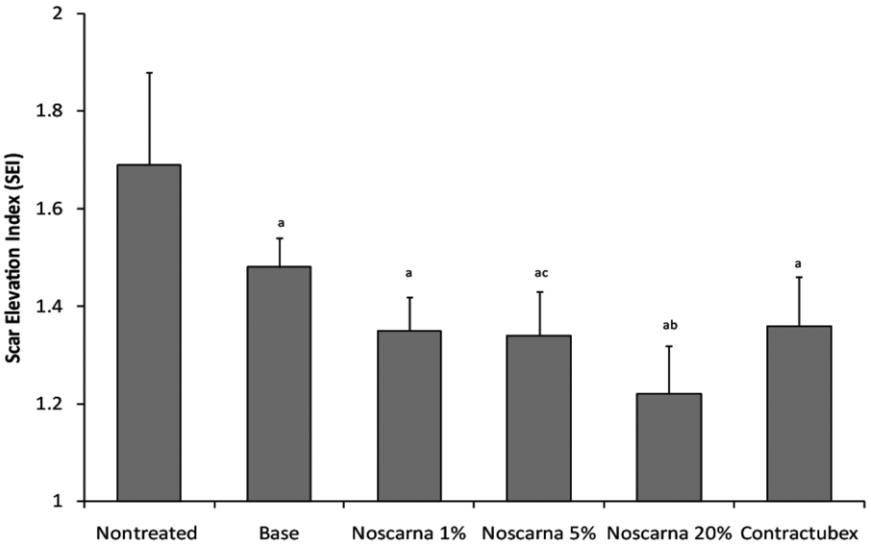

Fig. 3. Treatment of healed full-thickness wounds in the rabbit ear model. Treatment of hypertrophic scarring with Noscarna for 4 weeks (postwounding days 28 to 56) significantly reduced scar hypertrophy. Values are expressed as mean ± SD of six scars. $^{a}P < 0.01$ compared with the nontreated control by the LSD test. $^{b}P < 0.01$ and $^{c}P < 0.05$ compared with the base control by the LSD test.

extracellular matrix components. Hypertrophic scars can cause sensations of itchiness and pain, and erythema and pigmentation. In addition, they can potentially develop several complications such as secondary infections and skin tensions with cosmetic disfigurement.

Topical silicone gels have been used for decades for the prevention and treatment of hypertrophic scars. The products containing silicone are considered as the first-line therapies for hypertrophic scar management. Many animal model experiments are being carried out to develop products that have more potent inhibitory effects on hypertrophic scars.

A unique animal model of hypertrophic scarring in the rabbit ear has been shown to be similar to the human condition in terms of its histologic and visual appearance with respect to larger wounds, its response to steroids, and improvements in the degree of scarring with advanced age [Morris et al., 1997; Marcus et al., 2000; Saulis et al., 2002a]. In this model, SEI is regarded as an accurate and reproducible instrument for evaluating hypertrophic scarring [Morris et al., 1997; Marcus et al., 2000; Saulis et al., 2002a]. Higher SEI scores indicate a higher level of hypertrophic scarring. As shown in Figure 3, marked decreases in SEI values were detected in the base control compared with the non-treated control scars. Moreover, Noscarna 1%, 5%, and 20% favorably reduced the SEI compared with the base control in the descending order of Noscarna 20%, Noscarna 5%, and Noscarna 1%. Hence, this can be considered as direct evidence showing that Noscarna has favorable inhibitory effects on hypertrophic scarring.

Reepithelialization is initiated as soon as possible in order to provide a protective epidermal layer to prevent infection and excessive water loss. Adequate reepithelialization is important since scar hypertrophy is more likely to occur if wound closure requires more than three weeks [Deitch et al., 1983] and increases in epithelial thicknesses were detected in hypertrophic scars [O'Shaughnessy et al., 2009]. In hypertrophic scars, keratinocytes show increased proliferation and differentiation compared with normal scar keratinocytes [Machesney et al., 1998; Hakvoort et al., 1999], and induced collagen production in fibroblasts [Bellemare et al., 2005]. Furthermore, the inflammatory process has direct effects on normal and abnormal wound healing, and exaggerated inflammation was also found to be involved in hypertrophic scarring [van der Veer et al., 2009; Su et al., 2010]. Hypertrophic scar formation is an aberrant form of wound healing and is an indication of an exaggerated function of fibroblasts and an excess accumulation of the extracellular matrix during wound healing [Aarabi et al., 2007]. In hypertrophic scar tissue, fibrocytes are present in higher numbers compared with mature scar tissue [Yang et al., 2005]. Table 1 shows that all three of the different Noscarna formulations significantly decreased the epithelial thickness, collagen disorganization, and number of inflammatory cells and fibroblasts compared with the nontreated control and the base control in the descending order of Noscarna 20%, Noscarna 5%, and Noscarna 1%, which were all correlated with less hypertrophic scarring. These findings are consistent

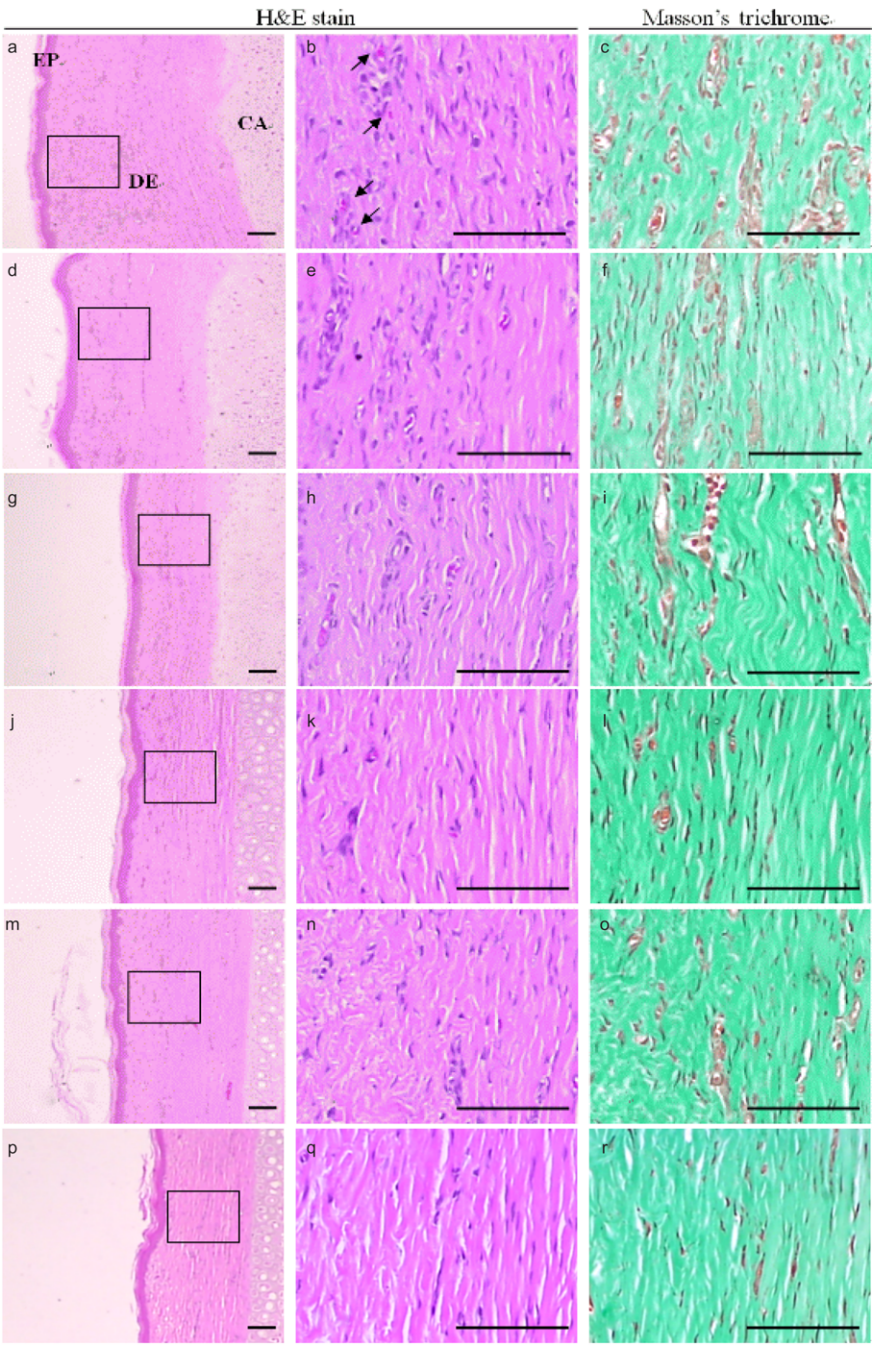

Fig. 4. The representative histopathological profiles of hypertrophic scars in the nontreated control (a~c), base control (d~f), Contractubex (g~i), Noscarna 1% (j~l), Noscarna 5% (m~o), and Noscarna 20% (p~r) groups. Squares indicate the enlarged areas in right columns. Arrows indicate vessels. Scale bars = 160 μm. EP, epithelium; CA, ear cartilage; DE, dermis. [Color figure can be viewed in the online issue which is available at wileyonlinelibrary.com]

with a decrease in pigmentation and SEI values. Thus, these results clearly show that the newly developed silicone based-gel formulation could be an effective treatment option in the prevention of hypertrophic scarring.

CONCLUSIONS

Silicone-based gel formulations containing allantoin, dexpanthenol, and heparin as the active ingredients displayed remarkable improvements in the healing

of hypertrophic scars and low levels of skin pigmentation in the rabbit ear model. The histopathological and histomorphometrical evaluation of the three different Noscarna formulations revealed marked or significantly decreased SEI values, anterior skin and epithelial thicknesses, collagen disorganization, and number of inflammatory cells, vessels, and fibroblasts compared with the nontreated control hypertrophic scars. Even though all three formulation of Noscarna favorably reduced the SEI, anterior skin, and epithelial thicknesses, collagen disorganization and number of inflammatory cells, vessels, and fibroblasts compared with the base-treated scars, this occurred in the descending order of Noscarna 20%, Noscarna 5%, and Noscarna 1%. These findings can be considered as direct evidence to show that Noscarna has potent inhibitory effects on hypertrophic scarring. In conclusion, silicone-based gel formulations containing allantoin, dexpanthenol, and heparin will be a promising therapeutic agent for the management of hypertrophic scars.

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