PERIOPERATIVE CONDITIONS AFFECT LONG-TERM HYPERTROPHIC SCAR FORMATION
ABSTRACT

Corticosteroids are widely used as treatment for excessive scarring by intralesional injection with variable success rates. It is conceivable that systemically administered corticosteroids affect a wider range of inflammatory processes that influence wound healing and may be more successful in preventing hypertrophic scar formation. To study this presumption, we have used a standardized model of presternal scars caused by cardiothoracic surgery through a median sternotomy incision. During cardiac surgery with cardiopulmonary bypass, 1 mg/kg dexamethasone was administered preoperatively, and 0.5 mg/kg 8 hours postoperatively. The presternal scars were evaluated prospectively 2, 4, 6, 12, and 52 weeks postoperatively at standardized measuring points. The height and width of the scars were measured 12 and 52 weeks postoperatively using both a slide caliper and a 7.5-MHz ultrasound probe. Cardiopulmonary bypass was used in 31 of the 43 participants. Eleven patients (35%) in the dexamethasone group developed clinical hypertrophic scars compared with four patients (33%) in the control group. These differences were not statistically significant. However, cranial scars became significantly wider in the dexamethasone group compared with the control group ($P = 0.04$). Twelve weeks postoperatively scars were significantly higher in the dexamethasone group, both cranial ($P = 0.05$) and caudal ($P = 0.03$). The differences in scar width and height were mainly present in patients that developed hypertrophic scars. The present results suggest that administration of high-dose perioperative dexamethasone does not prevent hypertrophic scar formation. Its use together with the cardiopulmonary bypass, however, did affect scar dimensions negatively up to 52 weeks after surgery. These findings contribute to the concept of the involvement of perioperative immunologic responses in the etiology of hypertrophic scar formation.

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INTRODUCTION

After every operation, trauma or burn injury the wound healing process will lead to scar formation, which protects the body against infection and excessive water loss. In some patients, these healing processes end with red, raised, itching hypertrophic scars or keloids, which are cosmetically displeasing, functionally discomforting, and impair quality of life\(^1\). The exact origin of excessive scar formation is still unknown\(^2\). For that reason, an established therapy to prevent the formation of hypertrophic scars and keloids is still lacking\(^3\).

A wide range of sequential processes are involved in hypertrophic scar formation. Platelets, macrophages, T lymphocytes, mast cells, Langerhans cells and keratinocytes are directly and indirectly involved in the activation of fibroblasts, which in turn produce excess extracellular matrix\(^2,4\). Currently, it is not known at what moment during wound healing the normal processes derail. Nonetheless, evidence is increasing that immunologic responses manifested shortly after wounding play an important role in hypertrophic scar formation\(^5,6\).

Corticosteroids have immunomodulating and anti-inflammatory effects by reducing pro-inflammatory cytokines, adhesion molecules, and inflammatory enzymes\(^7\). They are widely used as treatment for excessive scarring by intralesional injection\(^3,8\). Multiple studies have proven the efficacy of corticosteroids for treatment of existing hypertrophic scars\(^9\)–\(^11\). Considering all of this, the use of corticosteroids to prevent hypertrophic scar formation seems rational. However, recurrence rates of 9% to 50% are observed when corticosteroids are injected intralesionally subsequent to scar resection\(^3\). It is conceivable that systemically administered corticosteroids affect a wider range of inflammatory processes that influence wound healing and may therefore be more successful in preventing hypertrophic scar formation.

To study this presumption we conducted a prospective cohort study using a standardized model of presternal scars caused by cardiothoracic surgery through a median sternotomy incision. These scars have a high incidence of hypertrophic scar formation\(^12\). In our hospital, it is custom to administer dexamethasone systemically at high dose before and after cardiac surgery that necessitates the use of cardiopulmonary bypass.

PATIENTS AND METHODS

Patients older than 18 years and undergoing cardiothoracic surgery through a median sternotomy incision were assessed for eligibility of participation in the study. Excluded were patients living more than 60 km away from the hospital and patients who were not able to revisit the clinic for follow-up appointments because of their medical condition. The medical ethics committee approved the protocol and all the participants signed an informed consent form before onset of the study.

All operations were performed at the department of Cardiac Surgery of the University Medical Center Groningen. Cardiopulmonary bypass was used during surgery that required opening of the heart chambers and in case of coronary artery
bypass surgery on the lateral side of the heart to support the circulation during surgery. In those cases, 1 mg/kg dexamethasone was given preoperatively, and 0.5 mg/kg 8 hours postoperatively, to reduce the inflammatory effects of the cardiopulmonary bypass.

For follow-up, all patients were examined at the Department of Plastic and Reconstructive Surgery of the University Medical Center Groningen 2, 4, 6, 12, and 52 weeks postoperatively. At standardized measuring points (Figure 1), the presternal scars were clinically evaluated and scored as normotrophic or hypertrophic. Hypertrophic was defined as raised above skin level while remaining within the borders of the original lesion\textsuperscript{13}. Figure 2 shows the aspect of a normotrophic and a hypertrophic presternal scar. A patient was labeled hypertrophic if 12 or 52 weeks postoperatively

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**Figure 1.** Standardized measuring points were located at 8 cm from the most cranial border and 8 cm from the most caudal border of the presternal scar.

**Figure 2.** Photographs taken 52 weeks postoperatively. A, The aspect of a normotrophic presternal scar. B, The aspect of a hypertrophic presternal scar.
at least one part of his/her scar was classified as hypertrophic. Otherwise the patient was labeled normotrophic. The height and width of the scar were measured 12 and 52 weeks postoperatively using a slide caliper and a 7.5-MHz ultrasound probe (SSD-680 EX/STD, Aloka Co., Ltd., Japan) at 8 cm from the most caudal and cranial border of the scar.

Data analysis was performed using S-plus statistical software (Insightful Corp., Seattle, WA). Differences between groups were analyzed using the Mann-Whitney test. The Pearson χ² test and Fisher exact test were used to analyze the association between dexamethasone treatment and scar aspect. P ≤ 0.05 was considered statistically significant.

RESULTS

A total of 76 patients were included, of which 44 were able to complete the follow up of 52 weeks. These included 7 women and 37 men with a mean age of 58 years (range 37–76). Other patients discontinued due to their medical condition in the period between 2 and 4 weeks after surgery. Two patients underwent surgery for cardiac valve replacement, 2 for a heart defect, and 40 for coronary artery bypass surgery (see Table 1 for patient characteristics). One of the 44 included patients was discarded from the analysis because of erroneous and incomplete scoring during evaluations and rupture of sutures early after surgery. The resulting atypical development of this patient’s scar is shown in Figure 3.

Cardiopulmonary bypass was used in 31 of the 43 participants. These patients received 1 mg/kg dexamethasone preoperatively and 0.5 mg/kg 8 hours postoperatively. The patient characteristics in both groups were similar, as shown in Table 1. Up to 52 weeks postoperatively 11 patients (35%) in the dexamethasone group developed clinical hypertrophic scars compared with 4 patients (33%) in the

![Figure 3.](#) Graphs of width measurements in time showing the extent to which the scar measurements of patient 3 differ from the other measurements. A, The cranial scar segment. B, The caudal scar segment. Patient 3 was excluded from the analysis.
control group (Table 2). These differences were not statistically significant. In those cases in which the cranial part of the scar became hypertrophic, the caudal part became hypertrophic as well. A cranial hypertrophic scar without caudal hypertrophy was not seen.

To test for differences regarding scar width between the study groups the maximum width and the area under the curve of the scar width measurements in time were investigated. Plots of the scar width suggest that the dexamethasone group developed higher scar widths than the control group (Figure 4). The area under the curve is significantly larger in the dexamethasone group regarding the cranial scars \( P = 0.04 \), Mann-Whitney test), which gives evidence of the formation of wider scars in the dexamethasone treated patients. Figure 5 shows the distribution of the maximum width across the relevant strata. It suggests that the difference between both study groups is more marked in patients that developed hypertrophic scars. When comparing the dexamethasone and control group in terms of maximum width separately for normotrophic and hypertrophic patients, evidence was found that in the dexamethasone group scar width was more increased in hypertrophic patients \( P = 0.01 \), Mann-Whitney test) than in normotrophic patients \( P = 0.54 \), Mann-Whitney test).

Measurements of the scars with ultrasound also suggested differences between the dexamethasone and control group regarding scar height. The height of the scars

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<th>Control group</th>
<th>Totals</th>
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<td>Male/female ratio</td>
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<td>60 (49-67)</td>
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<tr>
<td>Weight, mean (range), kg</td>
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<tr>
<td>Length, mean, m</td>
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</tr>
<tr>
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<td>3 (25)</td>
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<tr>
<td>Allergy, No. (%)</td>
<td>5 (16)</td>
<td>3 (25)</td>
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Table 1. Patient characteristics of the dexamethasone group and the control group.

<table>
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<th>Totals</th>
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<tr>
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<tr>
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Table 2. Number of patients who developed hypertrophic scars in the dexamethasone group (who received high-dose dexamethasone perioperatively) and the control group (who received no dexamethasone perioperatively) up to 52 weeks postoperatively.

The Pearson $\chi^2$ test and Fisher’s exact test give no evidence of an association between treatment with dexamethasone and scar aspect ($P$-values of 0.82 and, 1 respectively).
**Figure 4.** Graphs showing the median series of width measurements of the scar segments in millimeters in the dexamethasone and the control group, the dashed lines representing approximate 95% confidence bands. A, The cranial scar segment. B, The caudal scar segment. Note that the scar width up to 6 weeks postoperatively is fairly similar in the 2 groups, and that differences increase greatly between 6 and 12 weeks postoperatively.

**Figure 5.** Boxplots comparing the distribution of the logarithm of the maximum scar width in the dexamethasone and control group. The patients in the dexamethasone group tend to have higher scar widths than the patients in the control group. This difference is statistically significant within the group of patients who developed hypertrophic scars. *P = 0.01, Mann-Whitney test.
12 weeks postoperatively was significantly higher in the dexamethasone group, both cranial \((P = 0.05, \text{Mann-Whitney test})\) and caudal \((P = 0.03, \text{Mann-Whitney test})\). Again, the differences were chiefly present in patients that developed hypertrophic scars (Figure 6).

**Figure 6.** Boxplots showing the distribution of the logarithm of the scar height (mm) 12 weeks postoperatively as measured by ultrasound. Patients in the dexamethasone group tend to have higher scars than the patients in the control group. This difference is statistically significant within the group of patients that developed hypertrophic scars, both cranial and caudal. \( ^* P \leq 0.05, \text{Mann-Whitney test} \).

**DISCUSSION**

In this prospective cohort study in 43 patients, systemic administration of high-dose dexamethasone perioperatively did not prevent hypertrophic scar formation. However, its administration together with the use of cardiopulmonary bypass significantly affected the ultimate scar dimensions in patients that developed hypertrophic scars.

Currently it is unknown at which exact moment the normal wound healing process derails and hypertrophic scar formation initiates. This makes the search for a treatment that prevents hypertrophic scar formation difficult, and consequently has kept many clinicians and scientists busy for decades\(^3\text{,}^{11} \). The results of this search, however,
have been fairly unsatisfactory. Advisory boards came up with recommendations that include the use of corticosteroids, silicone application, pressure, and radiotherapy as treatments for hypertrophic scars with scientifically proven effect\textsuperscript{11}. A preventive treatment, however, is still lacking.

Corticosteroids are widely used as a treatment for excessive scarring by intralesional injection and topical application with success rates varying between 50\% and 100\%.\textsuperscript{8-10,14} Corticosteroids decrease migration and activation of inflammatory cells and fibroblasts at the site of injury\textsuperscript{13,15-17}. They reduce expression of pro-inflammatory cytokines and profibrotic growth factors like transforming growth factor-\(\beta\), platelet-derived growth factor, and insulin-like growth factor-1\textsuperscript{18-23}. Consequently, glucocorticoids strongly interfere with the synthesis of type I and III collagen\textsuperscript{17,24}. Moreover, they suppress the regeneration of capillaries and epithelium, and reduce wound contraction\textsuperscript{16,21,25,26}.

Now that evidence is increasing that exaggerated (systemic) immunologic responses manifested shortly after wounding play an important role in hypertrophic scar formation\textsuperscript{2,5,6}, it is conceivable that, if administered at the right moment, systemic corticosteroid treatment may be suitable for preventing hypertrophic scar formation because of higher potency and higher tissue penetration.

Presternal scars caused by cardiac surgery through a median sternotomy incision have a high incidence of hypertrophic scar formation\textsuperscript{12}. Cardiac surgery with cardiopulmonary bypass is associated with a systemic inflammatory response, caused by cardiopulmonary bypass and surgical trauma\textsuperscript{27,28}. Contact between blood and the artificial surfaces of the extracorporeal circuit triggers inflammation and coagulation. It causes complement activation and damages several blood cell lines\textsuperscript{28,29}. Perioperative administration of dexamethasone is used to reduce early inflammatory processes, like increased capillary permeability and leukocyte migration. It is generally safe, reduces pain and swelling\textsuperscript{30,31}, and shortens hospital stay and time to recovery\textsuperscript{32}. In 31 of the 43 patients in this study, dexamethasone was perioperatively administered in high dose. No significant difference between both groups regarding incidence of hypertrophic scar formation was found. Interestingly, however, patients with hypertrophic scars in the dexamethasone group showed an increased width of cranial and caudal scars, and an increased scar height up to 52 weeks postoperatively compared with those of the control group (Figures 4-6). It thus appears that the perioperative conditions affect scar outcome up to 52 weeks after surgery.

Our data suggest that the systemically administered dexamethasone has not been effective in reducing the profibrotic inflammatory response at the wound site. Possibly, discontinuation of dexamethasone at day 1 initiated a rebound phenomenon with higher influx of inflammatory cells\textsuperscript{33,34}. Together with the systemic inflammatory reaction initiated by the cardiopulmonary bypass, this could have caused an induced inflammatory phase during wound healing, responsible for increased extracellular matrix deposition by fibroblasts. Furthermore, corticosteroids are known to stimulate the alternative activation of macrophages, which gives them profibrotic properties\textsuperscript{35}, thereby possibly increasing fibrosis in later stages of wound healing. In any case, the results suggest that modification of the early inflammatory response influences scar formation during the later stages of wound healing in patients that develop
hypertrophic scars. Further research is required to determine which perioperative inflammatory processes are responsible for this phenomenon and what their underlying molecular mechanisms are. This subsequently may lead to an effective treatment for the prevention of hypertrophic scar formation.

In conclusion, perioperative systemic administration of high-dose dexamethasone did not prevent hypertrophic scar formation. Its use together with the cardiopulmonary bypass, however, did affect scar dimensions negatively up to 52 weeks after surgery. These findings contribute to the concept of the involvement of perioperative immunologic responses in the etiology of hypertrophic scar formation.

ACKNOWLEDGEMENTS

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REFERENCES


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