Topical steroids for chronic wounds displaying abnormal inflammation

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ABSTRACT

INTRODUCTION Chronic, non-healing wounds are often characterised by an excessive, and detrimental, inflammatory response. We review our experience of using a combined topical steroid, antibiotic and antifungal preparation in the treatment of chronic wounds displaying abnormal and excessive inflammation.

METHODS A retrospective review was undertaken of all patients being treated with a topical preparation containing a steroid (clobetasone butyrate 0.05%), antibiotic and antifungal at a tertiary wound healing centre over a ten-year period. Patients were selected as the primary treating physician felt the wounds were displaying excessive inflammation. Healing rates were calculated for before and during this treatment period for each patient. Changes in symptom burden (pain, odour and exudate levels) following topical application were also calculated.

RESULTS Overall, 34 ulcers were identified from 25 individual patients (mean age: 65 years, range: 37–97 years) and 331 clinic visits were analysed, spanning a total time of 14,670 days (7,721 days ‘before treatment’ time, 6,949 days ‘during treatment’ time). Following treatment, 24 ulcers demonstrated faster rates of healing, 3 ulcers showed no significant change in healing rates and 7 were healing more slowly ($p=0.0006$). Treatment generally reduced the burden of pain and exudate, without affecting odour.

CONCLUSIONS In normal wound healing, inflammation represents a transient but essential phase of tissue repair. In selected cases, direct application of a steroid containing agent has been shown to improve healing rates, presumably by curtailing this phase. Further evaluation is required to establish the role of preparations containing topical steroids without antimicrobials in the management of chronic wounds.

KEYWORDS

Chronic wounds – Inflammation – Topical steroids – Wound healing

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Dogma has traditionally equated steroids with a reduction in the body’s capabilities to heal wounds. Evidence for this has been available for some time; administration of high corticosteroid levels in the early stages of wound healing was shown over 40 years ago to delay the appearance of inflammatory cells, fibroblasts, the deposition of collagen, the regeneration of capillaries, contraction and epithelial migration.¹ These wounds essentially fail to exhibit an inflammatory response.²

More recent studies have uncovered greater detail behind the negative wound healing qualities of corticosteroids.³ For example, glucocorticoids decrease the steady state levels of procollagen messenger ribonucleic acids (mRNAs) and mRNA synthesis in unwounded cells, thereby decreasing type I procollagen synthesis.⁴ The resultant wounds heal with incomplete granulation tissue and reduced wound contraction.⁵ Corticosteroids reduce transforming growth factor beta (TGF- β) and insulin-like growth factor 1 (IGF-1) production in wounds, both of which are vital for numerous factors during normal wound healing including col-

lagen production.⁶ Interestingly, retinoids are able to partially reverse this resultant reduction of TGF- β and IGF-1. Dexamethasone has been shown to inhibit the production of hypoxia inducible factor-1, a key transcriptional factor in healing wounds.⁷ Corticosteroids also increase the chance of a localised wound infection, thus retarding healing.⁸

Most wounds heal rapidly within days or weeks. Chronic wounds, defined as those that fail to heal within six weeks,^{9,10} may occur as a result of a variety of ulcer or patient-specific factors. Yet despite a marked heterogeneity among patients with chronic wounds, they are commonly characterised by an excessive inflammatory response, essentially getting ‘stuck’ in the inflammatory phase.¹¹ They are therefore associated with a greater number of inflammatory cells such as neutrophils, lymphocytes and macrophages.¹²

The resultant inflammatory milieu contains high levels of inflammatory cytokines, proteases (especially matrix metalloproteases [MMPs] and elastase) and reactive oxygen species,^{13,14} and low levels of protease inhibitors such as the tissue inhibitors of metalloproteases.^{15,16} This milieu

results in excessive degradation of the extracellular matrix and failure of progression of wound healing. This factor has been identified as one of the four key components of wound bed preparation (summarised by the acronym TIME: tissue, inflammation/infection, moisture, epithelial edge).^{10,17} From the above evidence, it would appear that aberrations in inflammation retard healing.

The use of topical steroids on a wound bed displaying evidence of excessive inflammation would therefore be a logical approach for treating such wounds. Case series exist of the successful use of topical corticosteroids for excessive granulation tissue following dermatological surgery but they are few and far between, and topical steroids have not become commonplace in general wound care.^{18,19}

In this article we review our unit's experience with Trimovate® (GlaxoSmithKline, Uxbridge, UK), a topical agent containing a steroid, antibiotic and antifungal (clobetasone butyrate 0.05%, oxytetracycline 3%, nystatin 100,000 units/g) in a variety of chronic wounds. This agent was used on wounds displaying excessive and abnormal inflammatory features despite receiving best clinical wound care. A combined preparation with antimicrobial effect was used, in preference to a single steroid agent, owing to the well-recognised observation that corticosteroid treatment typically increases infection risk.⁸ Healing rates were calculated for before and during Trimovate® treatment to identify changes in wound healing rates. Changes to wound-related pain, exudate and odour were also investigated.

Methods

A retrospective service evaluation review of all patients being treated with Trimovate® at a tertiary wound healing centre over a ten-year period was undertaken. Patients who had received Trimovate® were identified and their clinical records reviewed. Wounds were included regardless of aetiology. Trimovate® treatment was started by a senior wound healing physician in cases where the wound base was thought to show excessive inflammation. Patients were only started on Trimovate® if their wound care had been optimised, yet they were failing to show appropriate and timely healing. Not infrequently, the wound size was increasing prior to application. The presence of spreading cellulitis, underlying osteomyelitis, infected synthetic material, obvious localised wound infection requiring antibiotics, necrotic tissue, excessive slough, eschar or frank pus precluded patients from treatment.

During treatment, Trimovate® was applied sparingly to the ulcer bed at the time of each dressing change. Other dressings, topical treatments and compression garments were prescribed as appropriate. Periwound steroids were used for the treatment of eczema as and when required. In patients with multiple wounds, individual wounds were analysed separately. Patients were included if they had received standard wound care spanning a minimum of three consecutive clinic visits prior to the introduction of Trimovate® and had subsequently received Trimovate® for a minimum of three consecutive clinic visits immediately following this. This was to allow estimation of a 'before treatment'

and 'during treatment' healing rate for each patient (see below). Patients were excluded if:

- > Trimovate® had been given erratically (ie not over sequential clinic attendances) or stopped by another clinician
- > Treatment time prior to or following Trimovate® was less than three consecutive visits
- > Patients had received major intervention for their wounds that may significantly alter wound healing rates (eg surgical intervention, endovascular arterial procedures, skin grafting).

Data collected included:

- > Basic demographic data
- > Wound aetiology, as confirmed by the senior physician in charge of the patients' care
- > Length and width of target ulcer
- > Patient reported measures of wound associated pain (measured for severity and frequency), exudate volume and odour (present or absent). These measures were captured and recorded using our standard institutional scoring system outlined in Table 1.

Data analysis

Owing to variations in the timing of clinic appointments and therefore wound measurements, these longitudinal data were analysed as follows. A root transformation of the area was calculated for each visit ($\sqrt{\text{length (cm)} \times \text{width (cm)}}$) to allow subsequent linear data modelling (Fig 1a). Time (in days) between each visit was calculated and plotted against the squared area for 'before Trimovate®' and 'during Trimovate®' treatment (Fig 1b). A line of best fit for each patient was calculated for both before and during treatment, with the rate of healing (unit = cm/day, Fig 1c) being the gradient. The coefficient of determination (R^2) was noted for each treatment period. Differences in healing rates following application of Trimovate® were calculated.

When changes in healing rates were minimally different (defined as $\leq 0.0001\text{cm/day}$), this was considered to be non-clinically significant and recorded as 'unchanged'. This was an attempt to avoid overanalysis of minor differences arising owing to inter and intraobserver measurements of

Table 1 Categorical scoring system for the reporting of symptoms regarding exudate, pain and odour, as used in the Wound Healing Research Unit clinical records, Cardiff

Score	1	2	3	4
Pain frequency	None	Intermittent	At dressing changes	Continuous
Pain severity	Mild	Moderate	Severe	Non-evaluable
Exudate	None	Light	Moderate	Heavy
Odour	Absent	Present

wound size.²⁰ Differences between the two treatment periods were analysed using a paired two-tailed t-test (equal variance between groups confirmed with F-test).

Changes in patient reported outcomes were analysed as follows. Ordinal data only were considered (ie a pain severity of ‘non-evaluable’ was ignored). A mean of the reported outcomes for each patient/wound episode was used as a surrogate level of ‘average’ symptom burden. Time (in days) spent below this surrogate level was recorded for both treatment periods and divided against the total time recorded for each treatment period. A reduction in symptom burden is indicated by an increase in the resultant value following Trimovate® application and vice versa. This methodology assumed that the outcomes reported by the patients at each clinic visit were indicative of their symptomology until the subsequent visit.

Table 2 Ulceration aetiology of those included in the study

Aetiology	n
Rheumatoid leg ulcer	12
Venous leg ulcer	10
Abdominal wound	4
Mixed arterial and venous leg ulcer	3
Neuropathic foot ulcer	1
Pressure ulcer	1
Vasculitic ulcer	1
Surgical wound (leg)	1
Pyoderma gangrenosum	1

Data collection and analysis was undertaken in Excel® (Microsoft, Redmond, WA, US). A *p*-value of <0.05 was considered statistically significant.

Results

In total, 41 patients were identified who had received Trimovate® over the 10-year period. Approximately 325 new patients and 1,350 follow-up patients are seen in our tertiary centre over a 1-year period, implying that Trimovate® treatment was started in significantly less than 1% of all reviewed patients. Of these 41 identified patients, 16 did not meet the inclusion criteria, mostly owing to short-term or sporadic use of Trimovate®. This left 34 ulcers identified from 25 individual patients treated with Trimovate® that met the inclusion criteria. Details of ulcer aetiology are given in Table 2.

The mean patient age at the beginning of observed treatment was 65 years (range: 37–97 years). Overall, 331 clinic visits were analysed, spanning a total time of 14,670 days (7,721 days ‘before treatment’ time, 6,949 days ‘during treatment’ time). This equated to a mean of 432 days examined per ulcer episode (227 days ‘before treatment’ time, 204 days ‘during treatment’ time) over a mean of 10 clinic attendances.

Prior to treatment, all wounds were showing signs of delayed healing, with 17 of these wounds enlarging in size. After treatment, only seven wounds failed to respond clinically. Comparison between these two time intervals showed that following Trimovate® treatment, 24 ulcers had more rapid rates of healing, 3 ulcers showed no significant change in healing rates and 7 were healing more slowly. Overall, healing rates were significantly improved following Trimovate® treatment (mean change in root transformed wound area: -0.0122cm/day [0.00427cm/day before treatment, -0.00792cm/day following treatment], *p*=0.0006) (Fig 2). Of the 68 lines of best fit, 35 (51%, 15 before treatment, 20 following treatment) had an *R*² value of over 0.7, implying accurate linear modelling.²¹

When only these figures were used for subgroup analysis, overall healing rates continued to show a significant improvement following Trimovate® treatment (mean change in

Figure 2 Average change in wound area after collating data from 34 wounds. Wounds were typically enlarging prior to treatment (0.00427cm/day) and reducing in size with treatment (-0.00792cm/day). The mean root area of the ulcers at the point of starting Trimovate® was 3.73cm.

root transformed wound area: -0.0170cm/day [0.00745cm/day before treatment, -0.0095cm/day following treatment], $p=0.01$). Complete healing was seen in three ulcers.

Changes in patient reported outcomes (exudate volume, pain frequency, pain severity and odour) are shown in Figure 3. More patients noted an improvement in symptom burden following Trimovate® treatment with regard to exudate, pain frequency and pain severity. Odour was largely unchanged by Trimovate® treatment.

Discussion

In normal wound healing, inflammation represents a transient but essential phase of tissue repair. However, aberrations in the inflammatory response are often seen in chronic wounds. Limited data exist regarding the application of topical steroids to wounds showing signs of chronic inflammation. This study has shown that Trimovate®, a combination of a steroid, antibiotic and antifungal, generally promotes wound healing in a cohort of patients with chronic wounds with clinical evidence of excessive inflammation, and is generally associated with a reduction in wound-related pain (both frequency and severity) and exudate.

Evaluation of a novel topical treatment for wounds is difficult in the context of a retrospective study. We have compensated for the lack of a non-treatment arm by measuring healing rates prior to the application of Trimovate® as well as during it, similar to other authors' methodologies.²² Using such a comparison allows individual patient data to be analysed, which may identify both positive and negative effects of a treatment that would have been missed with a standard comparison of a non-treatment arm.

Figure 3 Changes in symptomology following treatment with Trimovate®. Treatment appears to reduce exudate and improve pain related outcomes while having minimal effect on wound-related odour.

A root transformation of the wound area was taken to allow construction of a simple linear regression model. Such calculations have been used in animal models, with impressive linear fitting.²⁵ It is generally assumed that healthy human wounds show an exponential reduction in surface area.²⁴ Despite this, exponential calculations have been shown to be inferior to more complex calculations in terms of modelling data from healing wounds accurately.²⁵ Furthermore, wounds that fail to follow an exponential decay model are significantly more likely to be chronic or hard-to-heal and the healing characteristics of such wounds are difficult to predict.²⁶

We selected a root transformation model for three reasons. First, this model is simple and can be easily reproduced by other researchers. Second, there were minimal differences in wound healing trajectories predicted by this model and by exponential modelling. Finally, as has been explained above, chronic wounds have not been accurately modelled to follow an exponential healing curve, and as many of the wounds were increasing prior to the application of Trimovate®, fitting an exponential decay curve would be, clearly, inappropriate.

Trimovate® generally reduced the pain (both frequency and severity) and exudate associated with these wounds. Excessive pain has been used as an indication for commencing topical steroid therapy previously.¹⁹ Inflammatory products (such as tumour necrosis factor, and interleukins 1B and 6) stimulate nociception and reduce pain threshold levels.²⁷ We suggest that the reduction in pain seen is a direct response of the reduction in inflammation.

In our cohort, a number of ulceration episodes were secondary to rheumatoid arthritis. Case reports do exist of steroid treatment for this type of ulceration, with minimal effects.²⁸ Separate analysis of this subgroup failed to show any significant difference in response to Trimovate® when compared with the remaining ulcers (data not shown). Such ulceration is characterised by an abnormal immune response, which is more complex than a simple increase in

inflammation.²⁹ However, Trimovate® may prove a promising topical treatment choice for these hard-to-heal ulcers.

Trimovate® combines a steroid, antimicrobial and antifungal, and is commonly prescribed for eczema or dermatitis.⁵⁰ The advantage of a combined preparation is that an antimicrobial theoretically reduces the risk of infection developing in an ulcer, which is potentially locally immunosuppressed by the topical steroids.¹⁹ Its antimicrobial effect may reduce the bioburden in the wound bed, thereby reducing inflammation.⁸ Furthermore, oxytetracycline may also play an anti-inflammatory role in addition to its antimicrobial action.⁵¹ Tetracyclines have been shown to reduce the production of MMP-2 and MMP-9 in vitro, and oral tetracyclines reduce MMP-1 production in an apparent dose-dependent manner.²² The precise role of tetracyclines on wound healing has not been described adequately and further research is required to evaluate how much of the healing effects of Trimovate® can be related to oxytetracycline.

Approximately 7–25% of chronic wounds contain fungi.^{52,55} The figure rises slightly to 27% in infected diabetic wounds requiring hospitalisation for treatment.⁵⁴ A study from 2012 has demonstrated that such patients show marked improvement in wound healing rates when treated with an antifungal compared with a best standard care control.⁵⁵ Such a response may be due to a reduction in the fungal burden but it may also be due to a subsequent reduction in detrimental bacterial effects. Fungi have been shown to have synergistic effects on bacteria,^{56,57} resulting in what Coulson *et al* describe as an ‘infective collaboration’.⁵⁸ It may well be that Trimovate® has part of its positive wound healing effect via its antifungal action.

Some caution is required when drawing conclusions from these data. Combined steroid, antimicrobial and antifungal treatment for ulcers is not without risk and we do not advocate its use as a panacea for all chronic wounds; in this patient population, 29% failed to respond to treatment. Although no significant adverse events were noted in our cohort, there is a potential for developing microbial resistance after protracted treatment. Furthermore, it is essential that the wound aetiology has been identified, and we would advocate a wound edge biopsy in wounds failing to heal with optimised conventional treatment prior to use of such an agent.

We would also suggest close follow-up of such patients by experienced wound healing physicians; our data show that although the majority noticed a marked improvement on Trimovate®, some patients’ wounds increased in size. In addition, we have studied a heterogeneous group of patients without a standardised control group and an RCT, ideally comparing multiple arms with different interventions, would be warranted to confirm the efficacy of Trimovate®. It would also be of vital importance to define objective and reproducible criteria for starting (and discontinuing) Trimovate® treatment.

Conclusions

This study has shown that a combined topical steroid, antibiotic and antifungal can improve wound healing rates

in a cohort of patients demonstrating abnormal inflammatory changes in their wounds. Furthermore, it can reduce exudate and pain symptoms. We propose that topical steroid treatment be considered in cases such as these although treatment should be given carefully, and only when a diagnosis has been made and there are facilities for subsequent close follow-up.

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