

Effect of Prednicarbate On the Hyper Proliferation of the Granulation Tissue of Traumatic Wounds During Directed Healing: A Prospective Observational Study

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Abstract

Background: The directed scarring of traumatic wounds in a surgical department often encounters drifts. During the proliferation phase, the granulation tissue can become excessive, blocking re-epithelialization and dooming a skin graft. To cope with this, healthcare teams often use topical corticosteroids such as Prednicarbate which is a non-halogenated corticosteroid which does not pass into the systemic circulation.

Purpose: The aim of this study is to describe the in vivo effect of Prednicarbate on the hyper proliferation of granulation tissue in trauma wounds and burns during directed scarring.

Methods: A prospective observational study was carried out on patients admitted consecutively to the Orthopaedic and Trauma Surgery Department of Aristide le Dantec Hospital in Dakar. The application of 0.25% prednicarbate was twice daily on the hyperproliferation areas of the wound bed of consenting patients. Demographic, clinical, therapeutic data and changes in granulation tissue were collected.

Results: 12 patients participated with an average age 41.5 ± 18.94 years and a female to male sex ratio of 3/1. Domestic accidents were the most common wound occurrence in 7 cases. After at least 3 applications, the modifications observed were as follows: the proportion of hyper-budding surface was reduced by 3% on average. In 8 cases, the bed turned pink, with a texture changing from smooth to granite in 10 cases. A regression of the edema of the bed was observed in all the cases and the level of the bed of the wound which initially known epidermal, became epidermal in 10 cases. In 10 cases, the start of epidermal migration was observed from the skin edges. In 9 cases, or 75% of cases, it took just 1 tube to see a reduction in granulation tissue.

Conclusion: Prednicarbate is a non-halogenated corticosteroid which is of interest in reducing the excessive proliferation of granulation tissue in traumatic wounds. By normalizing the level of granulation tissue, it promotes epidermal migration and the epithelialization phase.

Keywords: Directed healing, Granulation tissue, Hyper proliferation, Nursing, Prednicarbate

Introduction

Skin healing is a complex process aimed at restoring the structural and functional integrity of the skin after trauma. It begins with platelet hemostasis, clot formation and an influx of inflammatory cells under the influence of cytokines [1,2]. The skin can undergo various aggressions leading to an injury. A healing process must quickly take place so that it regains its barrier function. This dynamic healing process is classically described in three

interconnected phases: vascular and inflammatory, proliferative and remodeling [3]. The management of traumatic wounds and burns poses a real problem of scarring which must be directed in order to obtain a secondary scarring or a granulation tissue favorable to a skin graft [4, 5]. In the normal state, the granulation tissue of a proliferation wound has the following characteristics: red or pink, granite, clinically clean, bleeding on contact, level limited to the epidermis, with epidermal migration.

In case of hyper proliferation, it becomes smooth, edematous, with a level exceeding that of the cutaneous banks and without

epidermal migration. During directed healing, the granulation tissue may become hypertrophic as a result of tissue growth factors, which would block re-epithelialization and cause a possible skin graft to fail [6]. All this to say that excessive granulation tissue inhibits epithelialization and delays healing [7]. To fight against this drift of the proliferation phase, healthcare teams use mechanical abrasion which is traumatic, or silver nitrate creams or corticosteroids [8, 9]. This study aims to describe the in vivo effect of Prednicarbate on the hyper proliferation of granulation tissue in traumatic wounds and burns during directed scarring.

Methods

Study design

It was a prospective observational study carried out at the Traumatology Orthopedics department of the Aristide Hospital DANTEC in Dakar (Senegal) from January to December 2019. It concerned all hospitalized patients and those followed in the department for directed scarring of "a traumatic wound or a burn, having a hyper-burgeoning and supported by prednicarbate in local application. In other words, it was a question of describing the changes in the wound bed after application of the 0.25% prednicarbate cream dosed at 0.25% on the hyperbaric area. Recruitment was consecutively in the department including each new patient who met the inclusion and non-exclusion criteria. A validated collection form was used to record the data for each selected patient. The application of prednicarbate was twice daily and the timing of observation of the evolution of the wounds was fixed according to the program of care of the service. The course of the study did not interfere with the patient's care schedule. Data collection was carried out by qualified nurses under the supervision of a doctor. The ethics committee of Aristide Le Dantec hospital approved (Ethical approval number: 2019010216) this study and written informed consent was obtained from patients or their first-degree relatives. Patient confidentiality and protection of interests were maximized and no harm was done to any of the patients. 0.25% prednicarbate was given free to patients included in the study.

Participants

The participants in this study had the following inclusion criteria: traumatic wound with hyper proliferative granulation tissue and followed in the department for directed healing. Patients who presented the following criteria were excluded from the study: known allergy to prednicarbate, a contraindication to the use of topical corticosteroids (acne rosacea, perioral dermatitis, skin reactions linked to vaccines, manifestations of bacterial infections, parasitic, viral and fungal on the skin), patients followed for tuberculosis, syphilis and immunosuppression with HIV, patients with superinfected wounds, corticosteroid-related skin depigmentation, chronic ulcer.

Variables

Demographics

Baseline demographic data was obtained upon admission to the service. These data included: age, sex, occupation, date of accident, circumstances, previous comorbidities, etiology of the wound,

initial area and proportion of excessive budding, appearance of wounds before the application of prednicarbate, the associated lesions. The area of wounds was assessed according to the Wallace rule or using the patient's hand apple, considering that it represents 1% of body surface.

Changes in granulation tissue

A senior physician, who had clinical and experimental expertise in directed wound healing, trained three study nurses to collect data from the granulation tissue change checklist. These data were: the color of the granulation tissue (red, pink), the texture (smooth or granite), the edema of the bed (presence or absence), level of the wound bed (under epidermal, epidermal or supra-epidermal), epidermal migration (presence or absence).

Prednicarbate

Prednicarbate used was packaged in 30 g tubes in the form of a cream and dosed at 0.25%. The variables sought for prednicarbate were firstly the number of applications and the quantity of tube used to be able to reduce hyper proliferation. On the other hand, monitoring the occurrence or not of the following side effects: skin atrophy, telangiectasia's, stretch marks, skin irritation, hypertrichosis, depigmentation, infection, acne breakout.

Statistical Analysis

Data was captured and analyzed using Epi Info™ software version 7.1.5.2. The general characteristics of the patients were described using standard descriptive statistics. The mean values and standard deviations were calculated for the quantitative variables and the numbers and percentages for the qualitative variables.

Results

Patient characteristics

The purpose of this study was to describe the in vivo effect of Prednicarbate on the hyper proliferation of granulation tissue in traumatic wounds and burns during directed scarring. 12 patients participated. These were 3 men and 9 women with an average age 41.5 ± 18.94 years. Domestic accidents were the most common wound occurrence in 7 out of 12 cases (58.3%), followed by road traffic accidents in 2 out of 12. high blood pressure was the only co-morbidity found in 1 case.

The etiologies of the wounds found were 2nd degree deep burns in 7 cases, decay in 3 cases and a stab wound. Almost all of the wounds were located in the limb segments. As an associated lesion, one of the patients noted a fracture of the proximal 1/3 of the femur on an intermediate hip replacement.

All of these patients were followed for directed wound healing. 0.25% prednicarbate was applied after an average period of 44.5 ± 42 days (min = 17 days; max = 158 days) on areas of the wound bed with excessive budding.

The descriptive characteristics retained for the wound beds were: the surface of the wounds, the proportion of the hyper-swollen surface,

the color, the texture, the edema, the level of the granulation tissue and the epidermal migration.

Before the application of prednicarbate, the area of wounds were estimated to be approximately $11 \pm 5\%$ of the body surface. The average excessive budding area was estimated at $4 \pm 2.66\%$ of the body area. In 83.3% (10 cases / 12), the granulation tissue was red, with a smooth texture in 100% (i.e. 12 cases / 12). There was edema of the bed in 100% of the cases (12 cases / 12) and the level of the bed of the epidermal wound, therefore exceeding that of the cutaneous banks in 100% of the cases. In all cases, there was no epidermal migration from the skin edges (**Figure 1**).



Figure 1: Hypertrophic Granulation Tissue

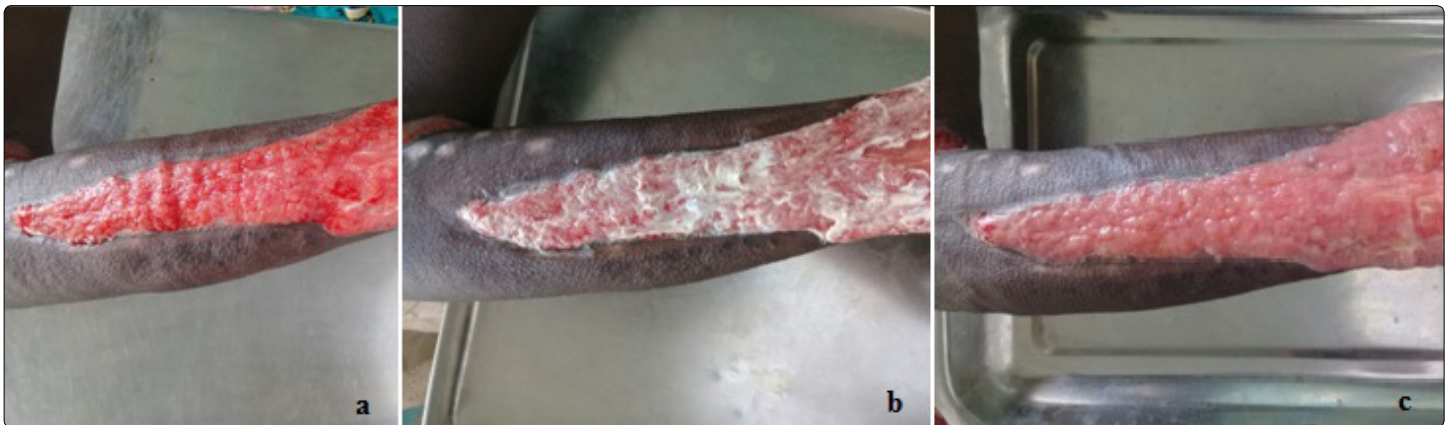


Figure 2: Modification of granulation tissue. a) Before application. b) Application. c) After 3 applications

Wound Healing

8 patients did not need a thin skin graft because they had spontaneous healing with favorable progress due to epidermal migration. Following the intervention, 4 patients benefited from a thin skin graft, the progress of which was favorable and without complications.

Sides Effects of Prednicarbates

The side effects of Prednicarbate were looked for throughout the study at each check-up. No unwanted side effects were observed by patients or researchers.

Granulation Tissue Changes After Application

The 0.25% prednicarbate was applied every 2 days to the areas of excessive budding, and a check was carried out before each re-application. The changes were noted. A modification of the granulation tissue was observed after an average number of 4.75 ± 4.85 applications, with a minimum of 2 and a maximum of 18. After at least 3 applications, the modifications observed were as follows: the proportion of hyper-budding surface was reduced by 3% on average. In 8 cases / 12, the bed became pink, for a texture changing from smooth to granite in 10/12. A regression of the edema of the bed was observed in all the cases and the level of the bed of the wound which initially exceeded that of the cutaneous edges, was balanced in 10 cases. Figure 2 illustrates a case. In 10% of cases, there was a beginning of epidermal migration from the skin edges. In 9 out of 12 cases or 75% of the cases, it took just 1 tube to have the effect described above. In 4 cases it took 4 tubes.

Discussion

The average age was 41.5 ± 18.94 years, an age group representing the active adult population who are more exposed to accidents. In this study, women were unemployed and looked after the household in the majority of cases. This explains the predominance of the female sex in domestic accidents, since cooking and domestic activities are exclusively reserved for the female sex in our societies. This observation was also made by Beyiha et al in the center of the burns of Douala [10]. The majority of wounds were caused by 2nd degree deep thermal burns.

The latter have the particularity of the alteration of the dermo-epidermic junction, exposing the dermis and explaining the preponderance of this etiology. Indeed, the dermis is a fibroelastic connective tissue which unites a cell contingent and an extracellular matrix. This cell contingent is mainly represented by fibroblasts, histiocytes and monocytes. Fibroblasts are responsible for the synthesis of macromolecules in the extracellular matrix which maintains the proliferative phase by developing [11]. Fibroblasts synthesize interleukin-1 α , a powerful inducer of fibroblastic proliferation which induces excessive budding of the wound bed [12, 13]. According to Chavoin, a hypertrophic granulation tissue is red, smooth and edematous. Its level exceeds that of the banks of the epidermis and there is no epidermal migration. A thin graft is doomed to failure [6].

All of these characteristics were found in all patients before the application of prednicarbate. The correction of these disorders was obtained after an average number of 5 local applications of 0.25% prednicarbate cream at 48 hours apart without any side effect. This is the first study to describe the effect of prednicarbate on connective tissue hyperplasia *in vivo*. It is usually indicated for the relief of inflammation and pruritus associated with corticosteroid-sensitive dermatological conditions, such as atopic dermatitis and psoriasis [14].

The application of local dermocorticoids to wounds has been known since the 1950s [15, 16]. In 1968, Ehrlich et al have already shown the beneficial effect of cortisone on the reduction of overburden in directed healing [17]. In fact, during the proliferative phase, corticosteroids reduce the secretion of TGF- β and the expression of KGF (Keratinocyte Growth Factor) secreted by mesenchymal cells which thus attenuate fibroblastic proliferation [18, 19]. However, the benefit / risk ratio of these corticosteroids varies from one molecule to another depending on its local ant proliferative action and its pharmacodynamics characteristics linked to their passage or not in the systemic circulation [20].

Prednicarbate is a non-halogenated corticosteroid derived from the double esterification of prednisolone which does not pass into the systemic circulation [21]. Lange et al showed *in vitro* that the best benefit / risk ratio of Prednicarbate compared to conventional corticosteroids did not only depend on its pharmacodynamics characteristics of non-halogenated but also on its specific action on the inhibition of interleukin-1 α , inducer of fibroblastic proliferation [22].

In addition, by comparing its *in vitro* action on epidermis and dermis cells, Lange et al showed that its inhibitory action on the synthesis of interleukin-1 α was significantly stronger than that of prednisolone, betamethasone and dexamethasone [22]. In this study, after at least 3 applications of 0.25% prednicarbate at a frequency of 48 hours or 3 times per week, the hypertrophic surface area decreased from 4% to 1% on average, a reduction of 75%. This result is superior to that of Spencer and Wagstaff who in a similar study on the effect of prednicarbate *in vitro*, showed a reduction in the thickness of the skin from 10 to 26% [23].

This difference can be explained by the role of chemical barrier of the skin and by a direct application on the granulation tissue in our study. In 2012, McShane et al reported 3 cases having had similar results in correcting the hyper proliferation of granulation tissue using 2 corticosteroids different from prednicarbate namely clobetasol 0.05%, Fluocinonide 0.05% [24].

However, this result was obtained after a greater number of 28 applications at a frequency of 2 times a day for 2 weeks. This study which describes the modifications of the granulation tissue of hyper proliferative wounds under the action of Prednicarbate has some limits. On the one hand, the results may not be generalizable to a larger population due to the sample size obtained by consecutive recruitment. On the other hand, to assess the effectiveness of this corticosteroid, a randomized study comparing its effect to a placebo would be indicated.

Conclusion

Prednicarbate is a non-halogenated corticosteroid which is of interest in reducing the excessive proliferation of granulation tissue in traumatic wounds. Its application, which was previously reserved for dermatological lesions, could be extended to the directed healing of wounds with an excessive budding phase. By reducing this excessive proliferation of granulation tissue, it thus promotes epidermal migration of the epithelialization phase and increases the chances of a successful skin transplant. A randomized study of its effect would be ideal for assessing its longer-term effectiveness.

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