

Case Report

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Keloid treatment: comparative intralesional injections of 5-fluorouracil, corticosteroid and 5-fluorouracil combined with corticosteroid

Tratamento de quelóide: comparação entre infiltrações intralesionais com 5-fluorouracil, corticosteroide e 5-fluorouracil associado a corticosteroide

ABSTRACT

Keloids are an excessive proliferation of dermal fibroblasts following a skin injury, which are difficult to treat. Isolated measures present a low rate of efficacy, while combined techniques lead to better results. A case of keloidal scar in the pubic region after a myomectomy surgical incision is described. The scar was divided into three parts, each of which was treated with intralesional injections of 5-fluorouracil, corticosteroid and 5-fluorouracil combined with corticosteroid.

Keywords: scar; keloid; therapy

RESUMO

O quelóide representa proliferação fibrosa exagerada da pele após injúria. É considerado de difícil tratamento, com baixa eficácia de medidas isoladas, demandando, na maioria dos casos, combinações de técnicas. Descreve-se caso de cicatriz queloidiana na região pubiana em incisão cirúrgica de miomiectomia. A cicatriz foi dividida em três partes tratadas com infiltração intralesional de 5-fluorouracil, corticosteroide e 5-fluorouracil associado a corticosteroide

Palavras-chave: cicatriz; quelóide; terapêutica

INTRODUCTION

Keloids are an exaggerated healing of the skin after injuries such as burns, surgical incisions, wounds, vaccinations, tattoos, hydradenitis and acne.¹⁻³ They are characterized by the uncontrolled growth of fibrous dense tissue beyond the borders of the original wound, without spontaneous regression, and tend to reoccur after being excised.^{1,2,4} Keloids often run in families, but their cause is unknown.^{1,2} Many patients complain about pruritus, pain, limitation of movements and their unattractive appearance.^{1,2,4,5} In spite of the lack of consensus on the lesion's development mechanism, the primary biochemical characteristic consists of the imbalance between the collagen's degradation and biosynthesis, resulting in the accumulation of fibrous dense tissue.^{3,6}

Keloidal fibroblasts produce much more collagen per cell than normal fibroblasts.^{1,5} Some studies, however, describe a great number of fibroblasts without a significant increase in collagen production, but with abnormalities in the proportions of

collagens I, III and IV. There are studies reporting a local increase in the collagenase inhibitor.² The abnormal response to the stimulation by transformer growth factor beta and cytokine's high levels are also implied in the pathogenesis.⁵

The treatment of keloids is thus based on the suppression of the fibroblasts' uncontrolled activity.^{4,6} There is no accepted universal treatment that leads to the complete correction of scars. Cryotherapy, intralesional corticosteroid (CE), occlusive bandage, compression, surgical excision, radiotherapy, laser and the use of antineoplastic agents, such as 5-fluorouracil (5-FU) intralesional, among others, are treatment options.^{3,4,7}

CASE REPORT

A Fitzpatrick skin phototype V 38-year-old female patient presented a 12 cm scar in the pubic region, after myomectomy. She had not received previous treatment.

The scar was divided into three equal sections and treated with intralesional infiltrations of 5-FU (right section), CE (left section) and 5-FU blended with CE (central section) so that the therapies could be evaluated separately (Figure 1). Five sessions, with intervals of around 30 days, were carried out. The right section was treated with 0.5 ml of 50 mg/ml 5-FU solution; 0.45 ml of 5-FU blended to 0.05 ml of 40mg/ml CE (a 9:1 proportion) was applied in the center; and 0.3 ml of 40 mg/ml CE was applied in the left section. Ulceration occurred in the isolated 5-FU infiltration area after the first session (Figure 2). The patient reported pain and a burning sensation in the infiltrations, especially when using the isolated 5-FU.

The parameters used to analyze the therapeutic response were: the patient's opinion regarding sensitivity, the reduction in tissue hypertrophy based on a visual inspection, and softening of the scar when palpated. Signs of good therapeutic response occurred after 4 CE applications, and 5 injections of either of the two other substances (5-FU + CE and isolated 5-FU). Minor hypochromias of the scar in the center (5-FU + CE) and in the left section (CE) were observed as adverse events.

DISCUSSION

Because it is an antimetabolite chemotherapeutic agent that interferes in the DNA and RNA syntheses, 5-FU could

limit the uncontrolled production of collagen fibers by the fibroblasts. In the beginning of the 1980s it was used in glaucoma surgeries to inhibit the scarring of the wound.² It has already been demonstrated that 5-FU inhibits the in vitro and in vivo proliferation of the fibroblasts.^{4,6} Its use in keloids was described both in isolation and in combination with other substances to reduce the monotherapy's treatment time and adverse effects.² In 1989, Fitzpatrick used 50 mg/ml 5-FU in keloids, with doses of 2-50 mg per session. Initially, monthly infiltrations were carried out, with unsatisfactory results. Subsequently, the frequency was changed to three times per week, with gradual and variable decrease², with intervals averaging one per week.^{2,4} While the 5-FU and anesthetic blend was ineffective in the control of pain,² the combination of 0.1 ml (10 mg/ml) CE with 0.9 ml (45 mg/ml) 5-FU presented effective results.² The 5-FU dose used in each application, as well as the interval between them and the number of sessions, varied among authors. Although side effects were more frequent with CE, Manuskiatti reported similar results using (50 mg/ml) 5-FU, 5-FU + CE (45 mg/ml + 1 mg/ml) and (20 mg/ml) CE in isolation in the treatment of keloids.⁶ Gupta used 50-150 mg per week and verified that the use of 5-FU is a safe and effective option for small keloids of short duration.¹ Nanda used doses ranging from 0.5-2 ml of 50 mg/ml 5-FU per session, for 12 weeks, with an improvement greater than 50% in most cases.⁴ Kontocheristopoulos employed 5-FU (50 mg/ml) weekly in doses of 0.2-0.4 ml/cm², with an average of 7 sessions and reports of recurrence.⁷ Asilian demonstrated that the combination CE (0.1 ml at 40 mg/ml) + 5-FU (0.9 ml at 50 mg/ml), applied weekly for eight weeks, was more effective, with faster results and fewer side effects than the isolated use of CE (10 mg/ml).⁵ The number of sessions varied from 5 to 10.2. Histologic analysis after the use of 5-FU demonstrated a decrease in the number of dense fibers and in the collagen's concentric nodular disposition, in addition to less prominent vascularization, pigmentary incontinence and decreased inflammation.^{6,7} Pain, a burning sensation, hyperpigmentation, purpura and ulceration are reported in the injection of pure 5-FU.^{1,4,6}

While studies demonstrate a direct relationship between the duration of the keloid and recurrence following treatment,



Figure 1: Keloid in the pubic region before treatment, divided into three sections for treatment with intralesional infiltration of 5-FU, CE and 5-FU + CE



Figure 2: Presence of ulceration in the area that received isolated 5-FU

no correlation could be drawn regarding its size.⁷ The oldest, hardest lesions, with little inflammation or few symptoms, present the lowest rate of response. The first signs of response are decreased pain and pruritus, followed by the softening of the scar and decreased erythema.² Treatment with intralesional 5-FU is safe and effective in the control of symptoms and recurring scars.⁸

Intralesional infiltration with corticosteroid is a well known and frequently used therapy for treating keloids.^{2,5} The wound healing process' suppression mechanism includes the interruption of the inflammatory process through the inflammatory cells' migration and phagocytosis inhibition, vasoconstriction resulting in the interruption of the flow of oxygen and nutrients to the wound, and antimitotic activity in fibroblasts and keratinocytes.² The inhibition of fibroblast proliferation is dose dependent. The used dosage varies from 10-40 mg/ml, with intervals of 4 to 6 weeks, until the scar improves.^{5,6} Adverse effects are atrophy, telangiectasias and pigmentation alterations.^{5,6}

The intralesional use of 5-FU + CE has been shown to be safe and effective in the treatment and prevention of keloids, and is a good option for patients who have already tried using CE without success.

CONCLUSION

In the present case, the best response was observed in the isolated use of CE, followed by the combination of 5-FU + CE, and pure 5-FU.

The isolated intralesional infiltration of CE offered greater benefits with fewer sessions, and produced an improvement of the clinical appearance and softening of the scar. Hypochromia was more evident in the isolated CE area and more modest in the area treated with 5-FU + CE (Figure 3). Treatment with 5-FU is not dismissed as an option, especially in cases that do not respond to CE. Due to controversy over the methods of its use and the respective results in the treatment of keloids, further studies about its efficacy, safety and the histological modifications linked to clinical results are necessary. ●



Figure 3: Scar in the pubic region after 4 infiltrations of CE in the left section, 5 infiltrations of 5-FU in the right section and 5 of 5-FU + CE in the center

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