A Controlled Clinical Trial With Pirfenidone in the Treatment of Pathological Skin Scarring Caused by Burns in Pediatric Patients

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Background: Pathologic skin scarring reversion remains a big challenge for surgeons, as disfiguring scars have a dramatic influence on patient's quality of life.

Methods: A controlled clinical trial was conducted to evaluate 8% pirfenidone (PFD) gel administered topically 3 times a day during 6 months to 33 pediatric patients with hypertrophic scars caused by burns. A total of 30 patients with hypertrophic scars with identical Vancouver Scar Scale values were treated with pressure therapy and included as controls. Improvements were evaluated by Vancouver Scar Scale and a Visual Analog Scale. Safety parameters were determined by the presence of adverse events and monitoring laboratory and hematology parameters.

Results: Patients treated with PFD during 6 months presented a continuous monthly statistically significant scar regression in comparison with the initial Vancouver measurement ($P = <0.001$). PFD group showed a higher improvement of all scar features as compared with control group treated with pressure therapy ($P = <0.001$). In the PFD group, 9 of 33 patients (27%) had their scores decreased in Vancouver classification by more than 55%, 22 patients (67%) had a 30% to 45% decrease, whereas 2 patients (6%) had a 30% decrease or less. Control group treated with pressure therapy showed a slight improvement in 16% of cases on an average. Patients did not show serious adverse effects or laboratory alterations throughout the study.

Conclusions: Topical administration of 8% PFD gel 3 times a day is more effective and safe in the treatment of hypertrophic scars caused by burns in children, as compared with standard pressure therapy.

Key Words: pirfenidone, burn scars, pathological skin scarring, Vancouver Scar Scale, scar regression, burns, scar, pediatric burns

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Pathologic skin scarring following surgical procedures, trauma, and specially burns is a great concern for patients and a challenging problem for clinicians, despite increased knowledge of wound healing.[1,2] Peacock defined hypertrophic scarring as a scar raised above the skin level that stays within the confines of the original lesion.[2]

Almost 15 million patients undergo pathologic scarring every year in the developed world.[3] Overall, 11 million hypertrophic scars and 4 million burn scars have been estimated, 70% of which occur in children.[4] This problem represents a major aesthetic, psychological, and physical problem around the world.

Various factors including location of injury and ethnic background may predispose a patient to development of keloid or hypertrophic scars; these can also appear with the stimulus of surgery, piercing, burns, lacerations, abrasions, tattoo placement, vaccinations, insect bites, and any inflammatory process such as acne, chickenpox, or folliculitis.[1]

Hypertrophic scars originate as a result of failure of normal wound healing.[5] Clinically, we now understand that hypertrophic scars remain confined to the borders of the injury and usually retain the shape,[6] which may have phases of reactivation and enlargement.[2]

The regular repair process of any given lesion consists of the following 3 phases: inflammation, proliferation, and remodeling, where a number of cytokines (transforming growth factor [TGF]-β, tumor necrosis factor [TNF]-α, epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF-1], etc) maintain the balance between degradation and biosynthesis of extracellular matrix (ECM) to obtain optimal tissue reparation or normal wound healing.[7,8] Routine degradation of ECM takes place by the action of matrix metalloproteinases, although the excessive synthesis of collagen, fibronectin, and proteoglycans along with a deficient ECM degradation and remodeling could render an abnormal skin lesion, which invariably results in the formation of either hypertrophic scars or keloids.[7] To date, there is no satisfactory treatment for these skin disorders.

Pirfenidone (PFD) is a wide-spectrum antifibrotic drug that modulates diverse cytokines action, involving TGF-β, TNF-α, epidermal growth factor, platelet-derived growth factor, VEGF, IGF-1, fibroblast growth factor, interferon-γ, interleukin (IL)-1, IL-6, and IL-8,[9–11] and it has shown promising effects in in vitro and in vivo settings. Also, PFD has proven effective in the prevention and regression of pulmonary fibrosis, peritoneal sclerosis, hepatic cirrhosis, uterine fibromyoma, left ventricular fibrosis, renal interstitial fibrosis, and breast capsular contracture in experimental models.[10–19]

Additional data in children with neurofibromatosis type 1 have shown that PFD is well tolerated in higher doses than those used in this clinical trial, with no evidence of dependency. Furthermore, no toxicity effects were noted and only minor adverse events that do not represent major health risks were present.[9]

On the basis of the evidence shown above, we conducted this controlled clinical trial to evaluate the efficacy of pressure therapy,

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which represents the most common therapy worldwide for scar treatment, compared with PFD gel, which represents a new therapy in the treatment of pathologic skin scarring caused by burns. Our results clearly showed that patients who received pressure therapy to treat their scars were less prone to obtain significant improvements in all scar features at the end of 6 months of this controlled clinical trial. Patients treated with 8% PFD gel underwent significant clinical improvements, measured using Vancouver Scar Scale (VSS) and Visual Analog Scale (VAS).

METHODS

Study Design

This open, controlled, prospective, and pilot clinical trial was designed to be carried out in 6 months duration to evaluate safety and efficacy of PFD (5-methyl-1-phenyl-2-[1H]-pyridone) gel at 8% concentration in the treatment of hypertrophic scars caused by burns from different etiologies. The medication was administered 3 times a day in the form of 8% gel manufactured according to good manufacturing practices (GMPs) and good laboratory practices (GLPs), and sanitary regulations enforced by the Federal Commission for Protection against Sanitary Risks.

Regulatory authorities and Ethics Committees from Hospital Civil de Guadalajara and the Federal Commission for Protection against Sanitary Risks approved the conduction of this protocol (along with patient information sheets and consent forms) with numbers 712/06 and 07330060100030, respectively. Also, this study was undertaken in accordance with the Declaration of Helsinki and with local laws and regulation applicable to the use of new therapeutic agents in Mexico.

All patients included were recruited at "Unidad de Quemados" (Burn Unit) from Nuevo Hospital Civil de Guadalajara. This Unit is a concentration center for this kind of disorders, which provides specialized medical care to pediatric patients from neighboring states to Jalisco, where the city of Guadalajara is located.

All procedures were informed to the parents of enrolled patients. Thus, the corresponding consent forms were signed before initiation of the protocol.

Patients enrolled in this clinical trial had scar evolution time ranging from 3 to 36 months and clinical characteristics of hypertrophic scars in PFD and pressure therapy were closely comparable. Psychological care was provided to parents and patients during the entire study.

Infection or systemic alterations (shock, renal or hepatic failure, etc) in postburn period were considered a reason for exclusion.

Study Group

A total of 33 pediatric patients with burn scar were enrolled for treatment with 8% PFD gel 3 times a day for 6 months, to evaluate the drug effect on the scar tissue.

Patients were clinically monitored on a monthly basis, with a complete blood test to evaluate presence of systemic alterations like infections, liver or kidney alterations, or something that could represent a nonexpected variable. After 6 months of treatment, the efficacy of PFD was determined clinically by using the VSS.

Pediatric patients included in this group were 18 males (55%) and 15 females (45%), with age ranged from 3 to 16 years (mean age, 7.03; standard deviation, ±3.56) who presented severe pathologic scars (VSS, 9–13 points) caused by burns, not previously treated with any kind of corrective treatment or drug. All patients enrolled had a scar evolution of more than 3 months. All patients had normal laboratory values for hepatic, renal, and serum levels at the beginning of the protocol and were followed up during the time of study.

Exclusion criteria applied to subjects who voluntarily withdrew to participate in this study. Also, patients were excluded because of the following reasons: important clinical abnormalities like sepsis, renal failure, or hepatic failure; violation of protocol; or investigators' decision due to medical or nonmedical reasons.

Control Group

In all, 30 patients were enrolled in the control group because they or their tutors chose not to take PFD. Instead, they decided to take the standard conservative treatment based on pressure therapy. This group was formed by 10 female (33.3%) and 20 male patients (66.33%), with age ranged between 4 and 13 years (mean age, 7.8; standard deviation, ±2.71). As the study group, these patients presented severe burn scars (VSS, 9–13 points), with a time of evolution of more than 3 months, and had normal values for hepatic, renal, and serum levels at the beginning of the protocol.

Therapeutic garment utilization was performed with a pressure therapy for at least 23 hours a day with a mean pressure of 30 mm Hg during 6 months, following international standard measures. In addition, a massage was applied using body lubricant cream t.i.d.

Patients were clinically evaluated on a monthly basis and were compared with PFD group at the end of 6 months.

Drug Administration

In the study group, 8% PFD gel was topically administered in the scar area as a thin layer before cleaning with neutral soap, t.i.d. (every 8 hours) for 6 months, making sure that the gel was absorbed by the skin, and waiting for around 20 minutes before clothing. Patient's compliance was closely monitored with drug registration sheets. Recommendations to avoid prolonged sun exposure were given to patients and their parents. Drug-related adverse events were monitored throughout the study.

Previous studies conducted by our research team on the pharmacokinetics and bioavailability of PFD gel in healthy subjects enabled us to propose the dose and frequency of topical application on hypertrophic scars.[11]

Clinical Assessment of the Scar

Clinical history and dermatological clinical assessment were elaborated by determining clinical characteristics of the scar based on VSS and VAS.

Vancouver Scar Scale

The VSS, first described by Sullivan in 1990 (Table 1), is perhaps the most recognized burn scar assessment method, which assesses the following 4 variables: vascularity, height/thickness, pliability, and pigmentation. Patient's perception of his/her respective scars is not factored into the overall score. The VSS remains widely applicable to evaluate therapy and as a measure of outcome in burn studies.[20–22]

Visual Analog Scale

The multidimensional VAS is a photograph-based scale derived from evaluating standardized digital photographs in 4 dimensions (pigmentation, vascularity, acceptability, and observer comfort) as well as contour. It sums the individual scores to get a single overall score ranging from "excellent" to "poor."[23–25]

Also, components and dimensions of the scar were assessed on monthly basis by a blinded internal panel composed by clinicians, plastic surgeons, and dermatologists to obtain standardized clinical assessment and calibrated digital images of the scars.

Statistical Analysis

Statistical analysis by repeated measures Analysis of Variance was used to prove the significant difference between basal VSS

TABLE 1. Vancouver Scar Scale for Burn Injuries[20]

Characteristic	Points	Measure
Pliability	0	Normal
	1	Supple
	2	Yielding
	3	Firm
	4	Adherent
Height	0	Normal
	1	1–2 mm
	2	3–4 mm
	3	5–6 mm
	4	6+ mm
Vascularity	0	Normal
	1	Pink
	2	Red
	3	Purple
Pigmentation	0	Normal
	1	Slightly
	2	Moderately
	3	Severely

and the next monthly measurements, whereas *t* test for paired samples and Mann-Whitney *U* test were used to compare Vancouver score between both groups (PFD and pressure therapy). The confidence interval used in this study was 99%. Statistical Package for Social Sciences 15.0 statistical program was used to analyze the data.

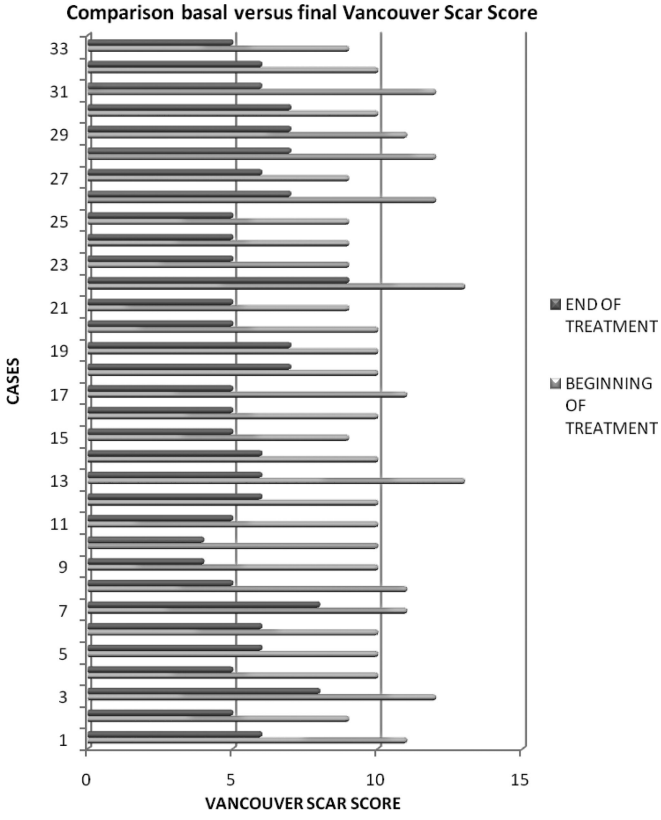


FIGURE 1. Patients were treated with PFD 8% gel and evaluated with the VSS before treatment and at the end of 6 months of treatment. A scar improvement in all cases, regardless of scar evolution time, is evident.

TABLE 2. Characteristics and Results of the Patients Enrolled

Epidemiology	PFD Group (n = 33)	Pressure Therapy Group (n = 30)
Patient's sex		
Men	18 (55%)	10 (33.3%)
Women	15 (45%)	20 (66.6%)
Age of the insult		
2–16 yr	Mean age = 7.03	Mean age = 7.8
	SD = 3.56	**SD = 2.71**
Causal agent of the insult		
Fire	20 (61%)	16 (54%)
Scald	10 (30%)	10 (33%)
Electricity	1 (3%)	0 (0%)
Contact with hot item	1 (3%)	4 (13%)
Gunpowder explosion	1 (3%)	0 (0%)
Improvement of the Scar at the End of Treatment	**PFD Group, n (%)**	**Pressure Therapy Group, n (%)**
Reduction (%)*	$P < 0.001$	$P < 0.001$
>55	9 (27)	0 (0)
30–45	22 (67)	0 (0)
<30	2 (6)	30 (100)
Serum Safety Levels	**Basal/Final**	**Average**
Hemoglobin (g/dL)	13.1/13.3	13.1
Platelets (per mm^3)	288515/310121	306788
AST (U/L)	25/26	25
ALT (U/L)	20/20	20

*This reduction was composed by the diminution of all features evaluated by Vancouver Scare Scale (VSS).

PFD indicates pirfenidone; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

RESULTS

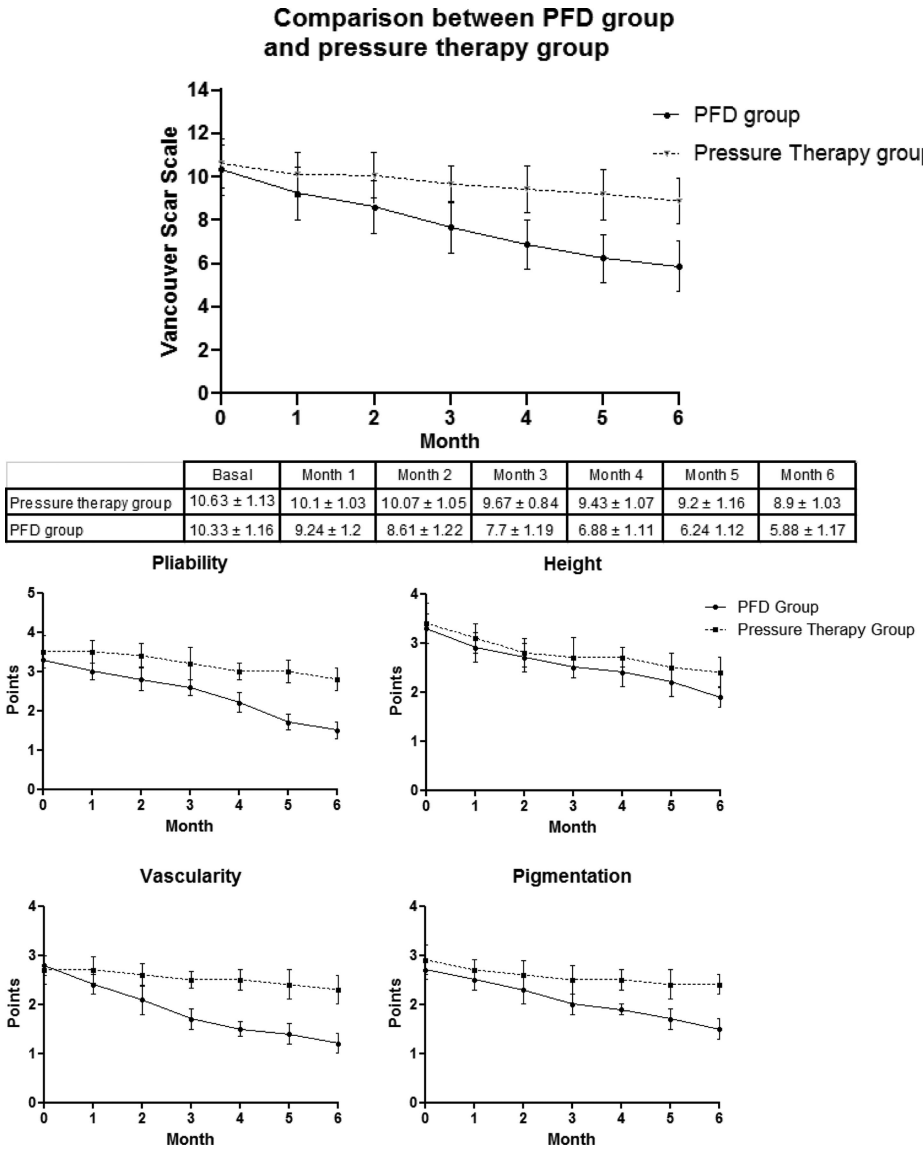
PFD Efficacy

Patients included in the study (n = 33) were treated with 8% PFD gel t.i.d., presented a minimum score of 9 and a maximum of 13 according to VSS, and presented a time of evolution from 3 to 36 months (average, 11 months) (Fig. 1, Table 2).

It is evident that scar improvement was observable and conspicuous on an individual basis. Also, data in this article are presented as average of multiple measurements even in complicated cases like burns in flexor surface of joints (shoulder, elbow, neck, wrist, knee, etc), which represents a more reliable demonstration of PFD efficacy (Fig. 2).

This study included 33 pediatric patients, 18 males and 15 females aged between 3 and 16 years who received the medication as described in the Methods section. As part of this controlled clinical trial, we evaluated 30 patients who received only pressure therapy.

Since the first month, patients in the PFD group presented statistically significant scar regression in comparison with the initial Vancouver measurement ($P = <0.001$). This scar regression was continuous and progressive month after month, until reaching the sixth month of treatment.



	Basal	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Pressure therapy group	10.63 ± 1.13	10.1 ± 1.03	10.07 ± 1.05	9.67 ± 0.84	9.43 ± 1.07	9.2 ± 1.16	8.9 ± 1.03
PFD group	10.33 ± 1.16	9.24 ± 1.2	8.61 ± 1.22	7.7 ± 1.19	6.88 ± 1.11	6.24 1.12	5.88 ± 1.17

FIGURE 2. Graphical representation comparing total and point-by-point VSS score between both the groups. We observed an improvement of 34% in PFD group than pressure therapy group at the end of the study. Comparative month versus VSS values showed statistical significance ($P < 0.001$).

The monthly comparison of scar regression between both groups showed statistical significance between the treatments. Patients treated with 8% PFD gel t.i.d. experienced a higher improvement in VSS and VAS scores at every month's determination, as compared with patients treated with pressure only. These differences were more noticed at the end of 6 months of the study ($P = <0.001$) (Fig. 2, Table 2). Representative photographs of 2 patients treated with 8% PFD gel are shown in Figure 3.

As indicated in the Methods section, patients were evaluated at the beginning, during, and at the end of the treatment, following the VSS and VAS. Parameters evaluated with VAS and VSS demonstrated a scar improvement, where 9 of 33 patients (27%) had decreased their Vancouver score by more than 55%, 22 patients (67%) decreased it from 30% to 45%, whereas 2 patients (6%) had 30% decrease or less (Table 2). Patients in pressure therapy experienced only a 16% average decrease in VSS clinical features.

PFD Adverse Effects

Patients who joined this study were followed up searching for systemic and blood abnormalities as indicated in the Methods section. Only minor adverse events like rash and local erythema in 4 of 33 patients (12%) were transiently present. These resolved on their own 1 hour after topical application of PFD.

PFD application did not induce any abnormal variation in laboratory parameters as indicated in Table 2 (aspartate aminotransferase, alanine aminotranferease, hemoglobin, and platelets).

Control Group

Thirty patients aged between 4 and 13 years were included in the control group and received a conventional treatment by pressure therapy. As indicated for patients enrolled in the PFD group, patients included in the pressure therapy were chosen to have an initial basal VSS ranging from 9 to 12 points (closely comparable with PFD group).

All these patients were included once the acute phase post burn injury had passed (3–6 months of scar evolution).

At the end of the study, patients treated conventionally showed a slight but significant improvement of 16% on an average ($P = 0.001$).

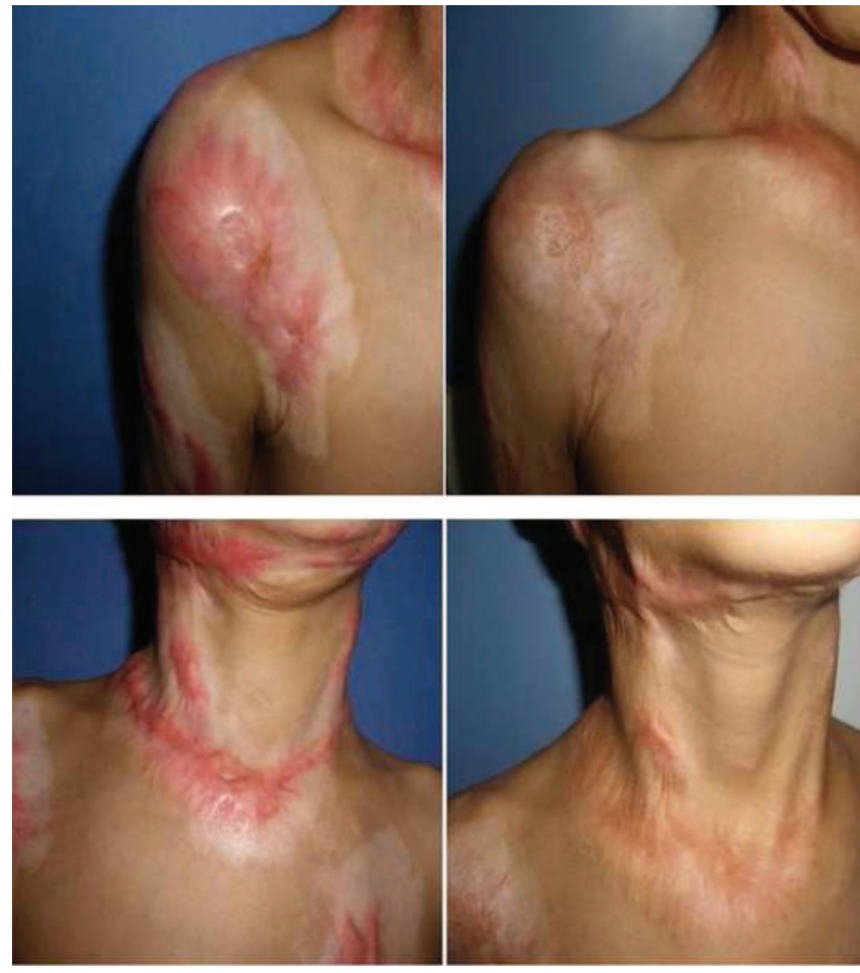


FIGURE 3. Representative digital image showing improvement in the parameters of VSS in 2 patients treated with PFD. Upper left panel shows a male patient with a 7 months evolution shoulder scar; upper right panel shows the same patient at the end of the study. Inferior left panel shows a 6 months evolution neck burn contracture; inferior right panel shows the same patient at the end of the study with PFD treatment as indicated in the Method section. A great improvement in the physical appearance and movement of the recovered neck was evident.

Representative photographs of 2 patients treated with conventional treatment by pressure therapy are shown in Figure 4.

DISCUSSION

The understanding of how postburn lesions activate an inflammatory cascade associated with liberation of mediators related with progression of the lesion, amplification of inflammatory response, and recruitment of immune/inflammatory cells, like TNF-α, TGF-β, IL-6, and monocyte chemoattractant protein-1 (MCP-1) has advanced increasingly.[26]

Our previous studies have found that PFD possesses a potent anti-TNF-α and anti-TGF-β action. This correlates with its potent anti-inflammatory action and the decrease in height and width of the scars shown in this study.[12]

Also, PFD has been shown to substantially decrease the expression of various collagens and other profibrogenic genes,[12,18] leading to stopping, controlling, and regression of collagen alterations in pathologic burn scars, and increment in collagen type I, decrease in the collagen type III, and reduction of the extracellular space and an increase in density.[27]

Pressure therapy is the treatment most commonly used by occupational therapist and physiotherapist since the mid 19th century and its properties to improve scars, no matter the time of evolution, have been proved across the time by clinical experience, but only few studies have been performed to evaluate its real efficacy. Thus, the use of pressure in the treatment of pathologic skin scarring still remains controversial, and even at present, no ideal treatment for this common skin ailment exists.[28,29]

Other treatments like surgery, silicon patches, radiation, brachytherapy, and intralesional steroids have been used to eliminate scars, unfortunately with poor results, variable adverse effects, and high recurrence rates.[8,18,30–32] Intralesional and topical therapies that act on a cellular level like mitomycin C, tamoxifen citrate, methotrexate, imiquimod and resiquimod, retinoids, calcineurin inhibitors, phenylalkylamine calcium channel blockers, botulinum toxin A, VEGF, basic fibroblast growth factor, hepatocyte growth factor, mannose 6 phosphate, interleukin-10, TGF-beta 3, antihistamines, and prostaglandin E2 had shown some promising results inducing the scar resolution.[33–52] However, most of those strategies are applied as preventive therapy, which makes difficult their use in the actual reversal of scars.

In this controlled clinical trial, we evaluated and compared the efficacy and safety of PFD in treatment of fibroproliferative problems like pathologic skin scarring presented in pediatric patients as a consequence of extensive burns, with a control group composed of patients treated with conventional pressure therapy. All patients enrolled in both the groups were considered in remodeling phase of wound healing with an evolution time ranging from 3 to 36 months and were considered if they were having mature scars. The total body surface area burned in the patients included was from 1% to 30%. The results we obtained proved efficacy of PFD in the treatment of pathologic skin scarring rendering a reduction of almost 60% in some patients in PFD group, whereas pressure therapy group presented a reduction of less than 16%

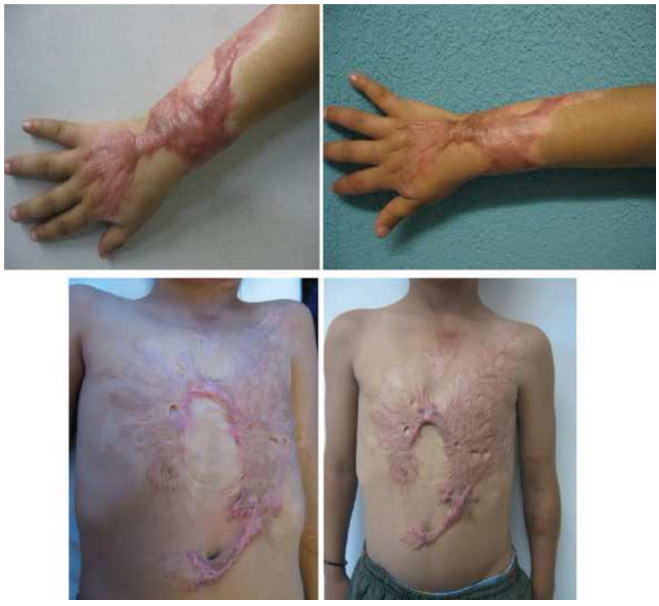


FIGURE 4. Representative photographs of 2 cases treated with conventional therapy (pressure therapy). Upper left panel shows a male patient with a 6 months evolution arm scar; upper right panel shows the same patient at the end of the study. Inferior left panel shows a 10 months evolution chest burn scar; inferior right panel shows the same patient at the end of the treatment with pressure therapy.

on an average, reflecting an advantage in the use of 8% PFD gel over the most common worldwide conservative therapy. The presence of scars in flexor joints presented the same range of improvement as the scars in other body surfaces.

Comparison between both therapies showed a significant scar improvement using pressure therapy or PFD, but the grade of improvement was higher in PFD than in the pressure therapy group. This fact represents an important evidence of PFD efficacy in the treatment of pathologic skin scarring.

All routine blood samples obtained from patients were tested and no evidence of alteration was reported. There was no change in the daily life for the PFD group, but avoidance of prolonged sun exposure was prescribed. Only minor side effects like pruritus, rash, and local erythema were reported by patients and their parents. They disappeared in the first month.

At the end of the study, we concluded that PFD is an effective and safe drug for treatment of fibroproliferative ailments including pathologic skin scars like the hypertrophic one. PFD may be used regardless of time of scar evolution or site of injury. Further studies are currently in progress to determine the action of PFD in acute burn healing phases.

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