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Reduced Postburn Hypertrophic Scarring and Improved Physical Recovery with Yearlong Administration of Oxandrolone and Propranolol

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Abstract

BACKGROUND—Massive burns induce a hypermetabolic response that leads to total body wasting and impaired physical and psychosocial recovery. The administration of propranolol or oxandrolone positively affects postburn metabolism and growth. The combined administration of oxandrolone and propranolol (OxProp) for one year restores growth in children with large burns. Here we investigated whether the combined administration of oxandrolone and propranolol for one year would reduce scarring and improve quality of life compared to control.

STUDY DESIGN—Children with large burns (n=480) were enrolled into this IRB-approved study; patients were randomized to control (n=226) or administration of OxProp (n=126) for 1 year postburn. Assessments were conducted at discharge and 6, 12, and 24 months postburn. Scar

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biopsies were obtained for histology. Physical scar assessments and patient reported outcome measures of physical and psychosocial function were obtained.

RESULTS—Reductions in cellularity, vascular structures, inflammation, and abnormal collagen ($p<0.05$) occurred in OxProp-treated scars. With OxProp, scar severity was attenuated and pliability increased (both $p<0.05$). Analyses of patient reported outcomes showed improved general and emotional health within the OxProp-treated group ($p<0.05$).

CONCLUSIONS—Here we have shown improvements in objective and subjective measures of scarring and an increase in overall patient-reported physical function. The combined administration of oxandrolone and propranolol for up to a year after burn injury should be considered for the reduction of postburn scarring and improvement of long-term psychosocial outcomes in children with massive burns.

MINI-ABSTRACT

Severe burn injury induces a hypermetabolic, hypercatabolic state, leading to inflammation, body wasting, scarring, and related morbidity that decrease quality of life. Here, we show that modulation of postburn metabolic dysfunction with the yearlong combined administration of propranolol and oxandrolone reduces scarring and improves related long-term outcomes.

INTRODUCTION

Severe burn injuries covering $\geq 30\%$ of the total body surface area (TBSA) significantly disrupt metabolism by inducing a hypermetabolic and catabolic state that leads to body mass wasting.¹ Mechanistically, this process is driven by hypercatecholaminemia,² an increase in cortisol and pro- and anti-inflammatory mediators, and futile cycling of substrates.³ Significant loss of lean body mass results, leading to debility and loss of physical function.⁴ Despite significant progress in delineating the causes and consequences of the hypermetabolic response, this state remains incompletely understood.⁵ However, studies suggest that modulation of postburn hypermetabolism both acutely and over the longer term improves outcomes.⁶ In addition to numerous non-pharmacologic strategies that have been developed to support the burn-induced hypermetabolic response, the current leading experimental pharmacological interventions for blunting postburn hypermetabolism and catabolism include the administration of propranolol or oxandrolone.

Propranolol is a non-selective β_1 and β_2 adrenoceptor antagonist that decreases heart rate and reduces hypertension in the general population. Based on the hypothesis that elevated catecholamines are responsible for the catabolic phenotype associated with burn injury,⁷ research began into the use of propranolol to attenuate postburn hypermetabolism.⁸ Since then, the benefits of postburn propranolol has included⁹ decreasing myocardial oxygen demand¹⁰, cardiac work^{11–13}, and peripheral lipolysis¹² without increasing the risk of sepsis¹⁴ or exacerbating altered immunity.¹⁵ Similarly, long-term propranolol administration decreased resting energy expenditure, heart rate, and central fat accretion while preventing bone loss and improving lean mass.¹⁶ When combined with participation in an exercise program, propranolol increased lean mass and aerobic capacity.¹⁷

Oxandrolone is a synthetic anabolic steroid hormone that is a less virilizing testosterone analog¹⁸ and is used to modulate postburn loss of lean mass.¹⁹ While oxandrolone had been used for its anabolic effects in other wasting diseases^{20,21}, use of this anabolic agent to curb the catabolism associated with burns began in the late 1990s.²² Early results suggested that twice daily oral dosing of 10 mg of oxandrolone, in combination with a high protein diet, significantly accelerated weight gain in the recovery phase following severe burns.²² Subsequent research showed that both younger and older groups of adult burn patients experienced a significant effect of oxandrolone treatment.²³ Next, the salutary effects of oxandrolone on body composition following burn injury were found to persist for at least 6 months after drug discontinuation, suggesting an extended benefit of the therapy.²⁴ In the acute phase following burn, oxandrolone decreases length of stay for adults²⁵ and may enhance erythropoiesis in children.²⁶ Although the duration of oxandrolone administration in adults was short, in children, the long-term administration of oxandrolone for up to one year postburn improved lean mass, lung function, and both bone mineral density and bone mineral content.^{27–29,30} The benefits of long-term oxandrolone administration persisted well beyond the duration of therapy in severely burned children as well.^{31,32}

Patients with large burns are at risk for developing pathologic scarring that is pruritic and inflamed and that limits movement and function; postburn hypertrophic scars affects 70-90% of these patients.³³ These scars continue to be a source of pain and discomfort and negatively impact quality of life for up to 2 years postburn.³⁴ Therapies such as laser or surgical revision can decrease the severity of burn scar.³³ However, there is a dearth of pharmacologic approaches that successfully reduce the effects of burn scars on function and quality of life after massive burns. One of the greatest risk factors for hypertrophic scarring following burn injury is delayed wound healing.³³ We have hypothesized that therapies that reduce wound healing time following a large burn, such as propranolol³⁵ or oxandrolone,³⁶ may also decrease hypertrophic scarring.

With declining mortality from burns, attention has naturally shifted to improving long-term quality of life.³⁷ To improve quality of life, we now focus on reducing the impact of scar and increasing physical activity.^{38,39} The chronic stress, inflammation, and catabolism in the first year following burn injury are likely to underlie negative outcomes.⁴⁰ Therefore, modulation of these chronic stressors would be reasonably expected to improve long-term outcomes in burn survivors. Previously we demonstrated that the co-administration of oxandrolone and propranolol (OxProp) for one year attenuated the burn-induced growth arrest in children with large burns.⁴¹ Based on the promising results of singly and co-administered oxandrolone and propranolol, we hypothesized that the yearlong OxProp administration to severely burned children would attenuate the development of hypertrophic scar, objectively measured in vivo scar characteristics, and overall patient-reported physical function.

METHODS

One thousand one hundred eighty-six eligible patients were admitted to Shriners Hospitals for Children®—Galveston between 2003 and 2015 (Fig. 1). Patients were between the ages of 6 months and 18 years at the time of burn, with burns over $\geq 30\%$ of TBSA, and required surgery for skin grafting after scald, flame, or electrical burn. This study, which is part of an

ongoing evaluation of the long-term administration of anti-adrenergic, anti-catabolic, or anabolic agents,^{8,11–14,17,19,28–32,35,41–60} was approved by the University of Texas Medical Branch Institutional Review Board ([ClinicalTrials.gov](https://clinicaltrials.gov) number, NCT00675714). Patients, or their legal caregiver if younger than 18 years of age, consented to participate in this trial; children between the ages of 7 and 18 assented to participate in the protocol as well. Patients were randomized to control (n=226) or OxProp for one year following injury (n=126); patients were assessed for up to 2 years postburn.

In the case of anoxic brain injury and/or when the decision was made to not treat because of injury severity, patients were excluded. Demographics, including age, sex, ethnicity, and burn size, were recorded at the time of admission. All patients received standard of care for inhalation injury, wound treatment, and nutrition as described previously.⁴¹

Patients allocated to Control were enrolled continuously from 2003 to 2017. Because of the balanced design of the randomization schedule for all patients participating in studies at Shriners Hospitals for Children®—Galveston (Fig 1), more patients were allocated to the Control group. Beginning in 2003, patients were randomized to OxProp; breaks in OxProp randomization were taken from 2005 to 2007 and 2008 to 2009 in order to randomize patients to the Ox or Prop groups. OxProp administration began within 4 ± 0.5 days following admission. Treatment group assignment was not revealed to the patients. Oxandrolone (BTG Pharmaceuticals, West Conshohocken, PA) was administered at a dose of 0.1 mg/kg every 12 hours for a minimum of 1 year; propranolol (Roxane Laboratories, Columbus, OH) was administered at a dose of 4.0 ± 0.2 mg/kg/day for a minimum of 1 year. The propranolol dose was titrated to decrease heart rate by 15%. Propranolol dosage was determined by a physician blinded to the patient's randomization.

Bradycardia was treated by holding a single dose of propranolol and recommencing administration 16 hours later with one half of the original dose. Over the next 24 hours, the propranolol dose was re-escalated to the original dose.

Tissue processing.

Scar samples were obtained during surgical revisions from a total of 30 pediatric patients (15 control, 15 OxProp) between 6 and 12 months following injury. Tissues were fixed in 10% neutral-buffered formalin, processed through absolute alcohol, and embedded in paraffin prior to sectioning at 4 μ m. Sections were then stained in hematoxylin & eosin (H&E) for histological scar assessments or processed for subsequent immunohistochemical (IHC) stains. Immunohistochemistry included staining for the beta-adrenergic and androgen receptors, through which propranolol and oxandrolone act, respectively. As previous studies have demonstrated that oxandrolone also inhibits the signaling downstream from the glucocorticoid receptor, staining was also performed for this receptor.⁶¹

Histological scar assessment and scoring.

Histology of scar H&E sections were evaluated using a scoring scale developed by a board-certified pediatric pathologist. Scarring parameters of circumscription, loss of rete ridges, epidermal thickening, inflammation, abnormal collagen distribution, and vascularity were assigned ordinal scores from 0 (none) to 4 (most severe). Tissue nodularity was assessed by

percent of scar area for each section. Three trained observers in scar histopathology then scored each section under microscopic evaluation (Olympus BX41) of the tissue. H&E sections were randomized and blinded to histopathology scorers prior to analysis. Subsequently, each section was digitized at 400× absolute magnification and gridded with a reticle to yield a 0.1 mm² area (version 1.12, Olympus DP22, cellSens software, Olympus Corp of the Americas, Waltham Massachusetts, USA). Tissue cellularity was quantified by counting positively stained nuclei in the papillary and mid dermis in 15 separate fields. For the scar assessment analysis, 6- and 12-month groups were combined.

Immunohistochemical analyses.

Tissues were processed as described above. Following sectioning, tissues were then deparaffinized and rehydrated. Antigen retrieval was performed in modified citrate buffer at pH 6.1 (DAKO target retrieval solution, Agilent, Santa Clara California, USA) and heated to 95°C for 15 minutes. To quench endogenous peroxidase activity, sections were exposed to 2% hydrogen peroxide diluted in methanol for 30 minutes and then washed in tris-buffered saline with 0.1% tween (TBS-T). Sections were blocked in 3% horse serum in TBS-T for one hour then incubated in primary antibody diluted in background-reducing antibody diluent (DAKO) at 4°C overnight. Negative controls received no primary antibody. Tissues were rinsed 3 times in TBS-T and then incubated in biotinylated secondary antibody for one hour at room temperature. After being washed 3 times in TBS-T, sections were further incubated in an avidin-biotinylated horseradish peroxidase (HRP) complex for 30 minutes and then exposed to hydrogen peroxide and diaminobenzidine (DAB) substrate (SK4105, Vector Labs, Burlingame California, USA) for 3 minutes.

The following primary antibodies were used for IHC: anti-CD31 (Abcam, ab199012, 1:250), anti-Ki67 (Abcam, ab15580, 1:1000), anti-glucocorticoid receptor (GCR) (Abcam, ab2768, 1:150), anti-alpha smooth muscle actin (α -SMA) (SigmaAldrich, A5691, 1:250), anti-beta2-adrenergic receptor (β 2-AR) (Abcam, ab182136, 1:100), anti-androgen receptor (Abcam, ab108341, 1:250), anti-collagen 1 (Abcam, ab138492, 1:250), anti-collagen 3 (Abcam, ab6310, 1:250). Secondary antibodies corresponded to the primary antibody host: biotinylated anti-rabbit IgG (PK6101, 1:150, Vector Labs) and biotinylated anti-mouse IgG (PK6102, 1:150, Vector Labs). IHC analyses for each tissue section included quantification by blinded observers of microvascular structures • mm⁻² by endothelial cell IHC for CD31, and α -SMA⁺ or Ki67⁺ fibroblasts • mm⁻², and scaled scores for tissue DAB intensity for β 2-AR, Col-1, Col-3, GCR, and androgen receptor staining from 0 (none to lightly intense DAB) to 4 (highly intense DAB).

Tissue scores for H&E scar assessments and immunohistochemical sections were averaged for all blinded observers. After unblinding, scores for control and OxProp groups were compared by a two-tailed student's t test using GraphPad Prism (version 7.03, GraphPad Software, La Jolla California, USA). Unless otherwise indicated, data is presented as mean \pm SEM; significant differences between groups were accepted at $p \leq 0.05$.

Modified Vancouver Scar Scale.

A trained clinician completed the modified Vancouver Scar Scale (mVSS)⁶². The mVSS is a validated tool that examines six parameters: pigmentation, vascularity, pliability, scar height, itch, and pain.⁶³ A total of 3,267 individual records were gathered; matching the data for time postburn resulted in 124 control and 57 OxProp-treated patients from 6-months to 9-years postburn. mVSS records with null scores, non-matched wounds, or unverified time points were excluded, resulting in 2,792 records for analyses. Normally distributed data differences in total mVSS score and individual mVSS parameters between treatment groups were assessed and compared for each time point by one-way analysis of variance (ANOVA). Data is represented as mean \pm SEM.

Patient and Caregiver Reported Outcome Measures.

The Burn Model Systems (BMS) National Longitudinal Database is a National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) funded, multi-center, longitudinal research project that includes patient reported outcome measures. These surveys assess emotional, social, and physical outcomes following burn injury, including measures of satisfaction with life, appearance, and scarring.⁶⁴⁻⁷⁷ The patients completed self-reported outcome measures, including Community Integration Questionnaire, the Satisfaction with Appearance Scale, the Burn Specific Health Scale, and in children 14+ years of age, the Short Form 12 (SF-12), at discharge and 6, 12, and 24 months postburn. Statistical significance was assessed with the Wilcoxon Rank Sum test using R version 2.3.2.⁷⁸

RESULTS

OxProp decreases cellularity, vascular structures, inflammation, and deposition of abnormal collagen in burn scars.

No significant differences were detected between the groups for age, burn size, sex, or length of stay. Histologically, scars from patients in the control group were more cellular (12.65 ± 0.45 cells $\cdot 0.1\text{mm}^{-2}$) than those in OxProp-treated patients (9.27 ± 0.33 cells $\cdot 0.1\text{mm}^{-2}$) ($p < 0.001$), suggesting a more physiologically active scar (Fig. 2a). Significantly reduced Ki67 expression in OxProp-treated scars (20.33 ± 3.13 Ki67⁺ fibroblasts $\cdot \text{mm}^{-2}$) compared to control scars (38.89 ± 8.43 Ki67⁺ fibroblasts $\cdot \text{mm}^{-2}$, $p = 0.039$, Fig. 2b) confirmed that cellular proliferation was greater in the untreated scars. The number of αSMA^+ fibroblasts did not vary between treatment groups (data not shown).

Expression of CD31, a marker of vascular structures, was reduced ($p < 0.0001$) with OxProp treatment, indicating significantly fewer microvascular structures in OxProp scars (10.56 ± 0.79 $\cdot \text{mm}^{-2}$) than in control scars (16.58 ± 1.301 $\cdot \text{mm}^{-2}$) (Fig. 3b). This finding may correlate with a lower vascularity score in H&E sections (1.45 ± 0.13 , control; 1.14 ± 0.12 , OxProp, $p = 0.087$, Fig. 3a); however, examination of more samples is necessary to determine whether a difference exists.

Dermal inflammation was reduced with OxProp treatment (scar score: 1.02 ± 0.09 ; $p = 0.0019$) compared to controls (scar score: 1.60 ± 0.16) in the papillary and mid-dermal

regions (Fig. 4a). Additionally, percent nodularity decreased ($p < 0.0001$) with OxProp treatment (control: $36.22\% \pm 4.41$; OxProp: $12.22\% \pm 3.33$) (Fig. 4b). Here we show that OxProp substantially diminishes ($p < 0.0001$) tissue histopathology scores for abnormal collagen deposition (1.28 ± 0.14) when compared to controls (2.25 ± 0.19 , Fig. 4c). Expression of collagen I and collagen III, however, was similar between treatment groups (data not shown).

OxProp treatment significantly increased glucocorticoid receptor expression in scar (Fig. 6). Scars from control patients expressed less glucocorticoid receptors in dermal fibroblasts (tissue score: 1.43 ± 0.20) than those from OxProp-treated patients (tissue score: 2.20 ± 0.22) ($p = 0.043$). Differences were not found in expression of the $\beta 2$ -AR or the androgen receptor (data not shown).

OxProp reduces severity of hypertrophic scarring in severely burned patients

Mean mVSS total scores were reduced in OxProp-treated patients over time, most significantly at between 6 and 12 months postburn ($p < 0.05$) compared to the control patients. In OxProp-treated patients, mVSS scores were reduced from 8.8 ± 0.2 to 6.4 ± 1.0 compared to control patients, 8.5 ± 0.3 to 7.5 ± 0.5 . OxProp showed the most significant reduction in total mean mVSS from 6 to 12 months (-2.4 ± 0.5 , $p = 0.02$) compared to control (-0.99 ± 0.3) (Fig. 5). One individual mVSS parameter, pliability, was significantly greater with OxProp ($p < 0.0001$, Fig. 7). No other individual mVSS scar parameters changed significantly.

Patient-reported physical function is improved with OxProp

We evaluated answers to questions on the questionnaires that addressed activity, overall health, and extent of physical or emotional limitations (TABLE 2). The control group contained 115 patients; the OxProp group contained 58 patients. There were no significant differences with respect to age, percent TBSA burned, percent third degree TBSA burned, or length of stay. When asked "How often do you perform leisure activities (movies, sports, restaurants)?" patients treated with OxProp reported significantly greater participation in activities at 2 years ($p = 0.007$). Patients completing the SF-12 reported better general health at 2 years ($p = 0.049$) compared to controls. When asked how often participants accomplished less than they would like because of emotional problems, the OxProp group reported that the frequency of emotional limitations was reduced significantly ($p = 0.018$) two years post burn. Finally, OxProp patients reported significantly better overall mental health as measured by the SF-12 Mental Health composite score at two years when compared to control ($p = 0.0012$).

DISCUSSION

In this prospective, randomized, double-blind, controlled study of the yearlong co-administration of OxProp following severe burn injury in children, we have shown improvements in both objective and subjective measures of scarring and an increase in overall patient-reported physical function. These results demonstrate benefits of the long-term, combined administration of propranolol and oxandrolone. The present findings add to

the already established benefits of the individual administration of oxandrolone and propranolol, in addition to the improved growth with the combined therapies^{8,10,12–15,17,19,26,28–32,35,41,43–47,49,50,52,79–81}.

From our histological analysis, we hypothesize that OxProp reduces postburn scarring via several potential mechanisms. First, dermal fibroproliferative capacity is reduced with OxProp treatment, as shown by the decrease in overall cellularity of the scar tissue treated with OxProp. The persistent decrease in Ki-67–positive cells at 12 months indicates that the proliferative capacity of deep dermal fibroblasts is reduced longitudinally with OxProp treatment. We previously demonstrated that propranolol changes β -AR expression and trafficking in scar dermal fibroblasts, providing precedence supporting direct action of propranolol on this cell population.⁸² Taken together, these findings may indicate that the scar matures faster with OxProp such that the scar is less physiologically active at the time of assessment. Next, we identified an overall reduction in blood vessels as detected via CD31 expression, suggesting that OxProp decreases angiogenic potential in postburn scars. This data also supports the contention that OxProp results in a less physiologically active scar, as fewer blood vessels correlate with reduced metabolic activity. Currently, there is a dearth of investigations into oxandrolone's effect on angiogenic potential; however, several studies show that propranolol suppresses neovascularization.^{83–85} Therefore, the anti-angiogenic effect shown in this study may be primarily induced by propranolol, although more investigations into the mechanism of action of oxandrolone are needed. The histological findings from our study have suggested mechanisms that may be responsible for the reduction in hypertrophic scarring with OxProp. In light of the changes in angiogenesis as detected by histology, we are now using laser speckle to assess blood flow through the scar to reduce the subjective nature of our assessments of blood flow / vascularity in burn scar.

We have also found that OxProp reduces dermal inflammation, nodularity, and abnormal collagen deposition. Twelve months following burn injury, OxProp diminished the severity of inflammatory cell infiltration within scars. Previous studies have concluded that both oxandrolone and propranolol alone can reduce collagen production through androgen receptor signaling perturbation⁸¹ and β -AR antagonism, reducing VEGF expression.^{86,87} This further supports the hypothesis that OxProp treatment may improve wound healing and reduce scarring following burns. Collagen I or III presence was not different as assessed by immunohistochemistry. Future analyses will be focused on the expression of other extracellular matrix proteins or activity of proteins that modify or breakdown collagen. Additionally, we found that OxProp increases glucocorticoid receptor expression, which may be a compensatory response to glucocorticoid antagonism through an androgen receptor-dependent manner.⁶¹ Further study into the relationship among adrenergic blockade, androgen supplementation, and glucocorticoids is warranted.

The decrease in mean mVSS scores showed an overall reduction in scarring with OxProp administration. The change in pliability with OxProp indicated reduced stiffness of the tissue so that the scar was more flexible and moveable. This finding correlates well with our histological findings that abnormal collagen deposition was reduced.

From our analyses of patient-reported outcome measures, we conclude that the long-term co-administration of OxProp improves recovery from burn injury. The data show that patients treated with OxProp believed that their health was better and engaged in leisure activities more frequently than their counterparts in the control group. By two years post injury, significantly more patients treated with OxProp were participating in activities. Patients on OxProp self-reported less frequent emotional limitations at 2 years postinjury than did the controls. The patients in the treatment group were also found to have greater improvement in mental health. These findings may result from improved healing with OxProp—these patients have resumed growing⁴¹ and have more lean mass and muscle strength²⁸; this would translate directly into an easier ability to function, allowing the patient to resume more daily activity and improving mental outlook.

A limitation of the study is the younger patient group who participated only in the quality of life questionnaires; these patients also had smaller burns. Even though these burns were smaller with a shorter length of stay, the outcomes were still better for patients treated with oxandrolone.

While we have suggested several hypotheses as to the mechanisms underlying the ability of co-administration of propranolol and oxandrolone to improve hypertrophic scarring and physical function, several alternative possibilities deserve mention. First, amelioration of the long-term adrenergic stress associated with burns improves anthropometric measures, specifically lean mass,¹⁶ as does treatment with oxandrolone.³² This increase in lean mass, when contrasted with the muscle catabolism of untreated patients, contributes to an overall increase in functional strength,²⁸ thereby increasing physical function.⁸⁸ Since patients treated with the combination of oxandrolone and propranolol reported improved general health, perhaps the increase in activity level creates a beneficial effect on scar tissue, such as the scar being stretched more because of increased activity. Alternatively, given that dermal fibroblasts proliferate in response to catecholamines, the excessive adrenergic stimulation after burn injury could lead to hyperproliferation within the developing scar.⁸⁹ Therefore, modulation of the persistent adrenergic stress associated with burn could decrease the activation of cutaneous fibroblasts, leading to a decrease in scar tissue formation.

CONCLUSION

Given the increasing evidence for the salutary effects of combined beta-blockade of burn-related hypermetabolism and the use of anabolic agents to blunt catabolism and increase anabolism, we conclude that the long-term administration of oxandrolone with propranolol should be considered for the treatment of pediatric burn survivors. The benefits of this combined treatment strategy, including resumed growth, increased muscle mass, greater strength, and now reduction in scar and greater activity, suggest that OxProp may be the most efficacious modulator of the hypermetabolic response that we have tested in burned children. Although long-term treatment of burned adults with oxandrolone has not been trialed, our reports of beneficial effects of OxProp suggest that this combination should be trialed in adults as well.

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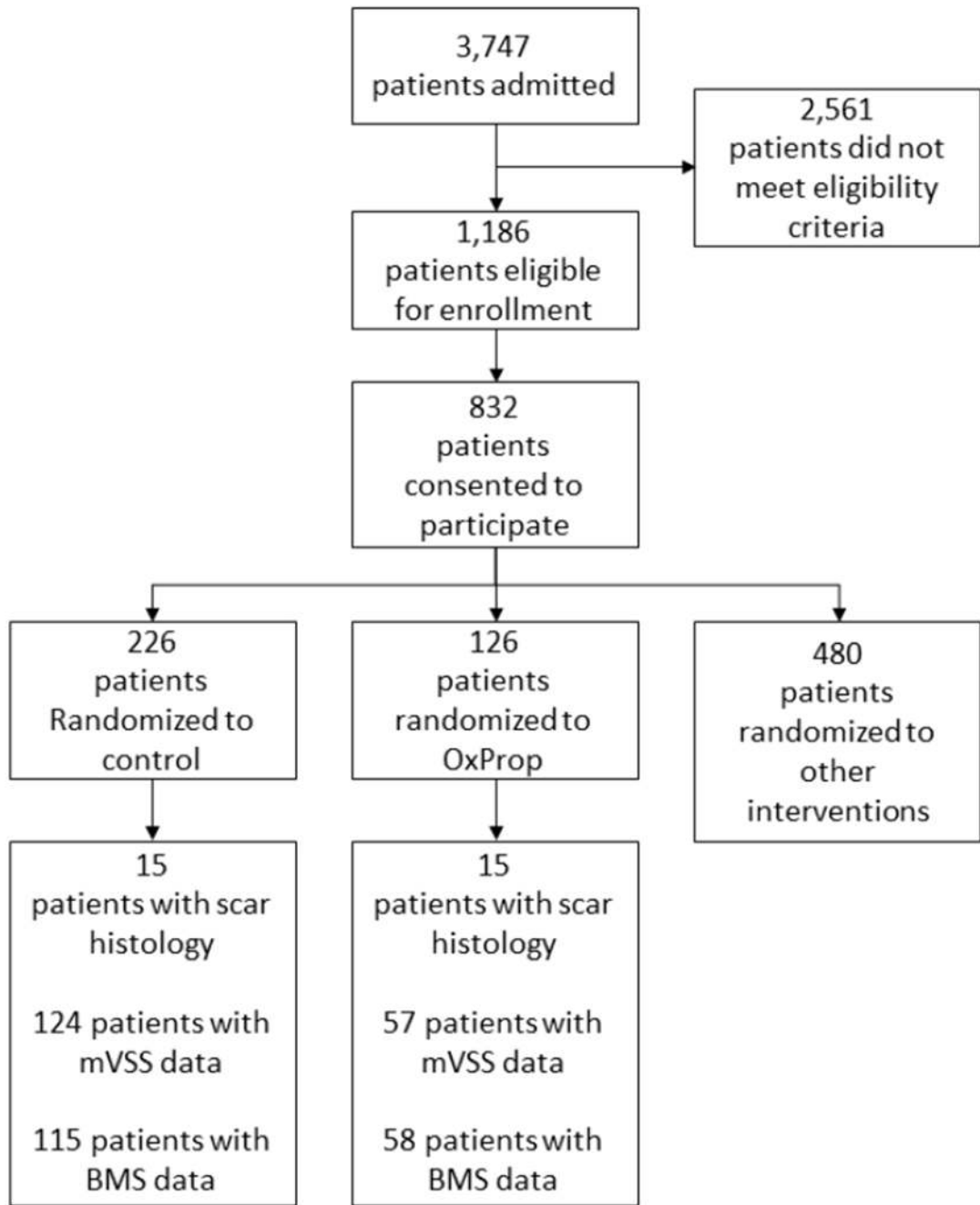


Fig 1.
CONSORT diagram

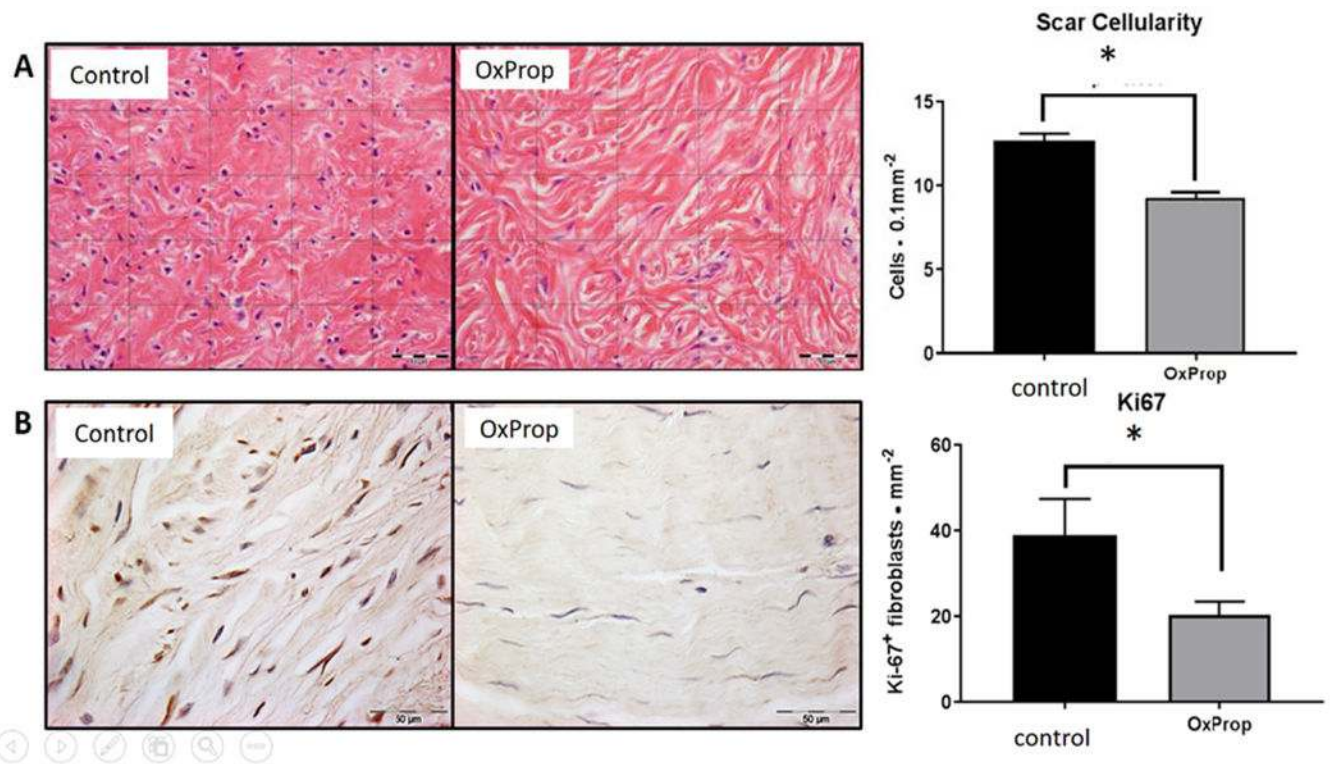


Fig 2.

OxProp treatment reduces scar cellularity and dermal fibroblast proliferation. (A) Representative images of H&E stained pediatric scar tissue after 12 months of control or OxProp treatment with associated quantification. When compared to control, scars from OxProp treated patient scars show significantly decreased dermal cellularity (* $p < 0.001$). (B) Ki67 immuno-stained sections of pediatric scar tissue 12 months postburn and accompanying quantification per mm^2 . OxProp treatment significantly lessens the proliferative capacity of dermal fibroblasts (* $p = 0.0392$) compared to control patients. Scale bars = 50 μm .

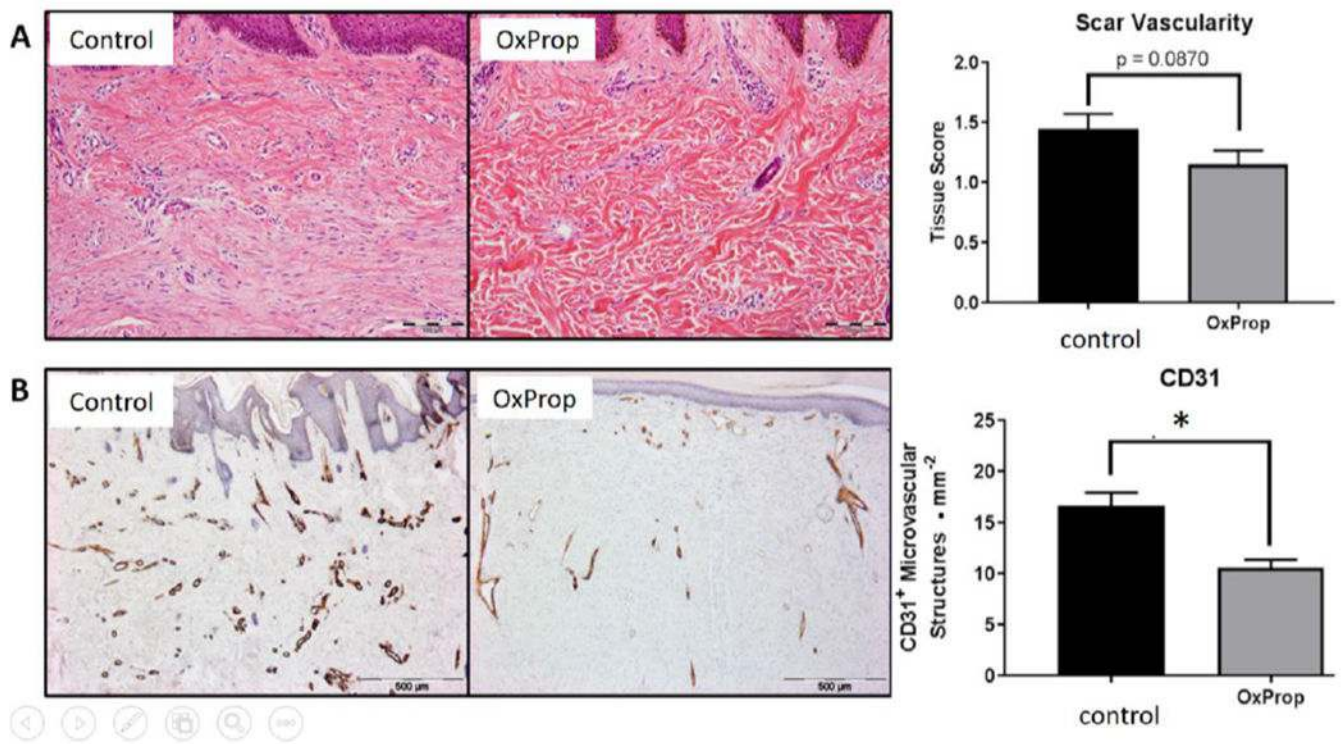


Fig. 3. OxProp mitigates angiogenic potential in post burn scars. (A) Representative H&E images of 12-month postburn treated scars with associated quantification. Scale bar = 100 μm . Tissue score show decreased vascularization in OxProp treated patients' tissues compared to control ($*p = 0.087$). (B) DAB immunostained scar sections after 12 months of injury and treatment with accompanying quantification Scale bar = 500 μm . CD31 expression is significantly decreased ($*p < 0.0001$) in scars of patients treated with OxProp compared to control after 12 months indicating significant reduction in neo-vascularization during the postburn wound healing process.

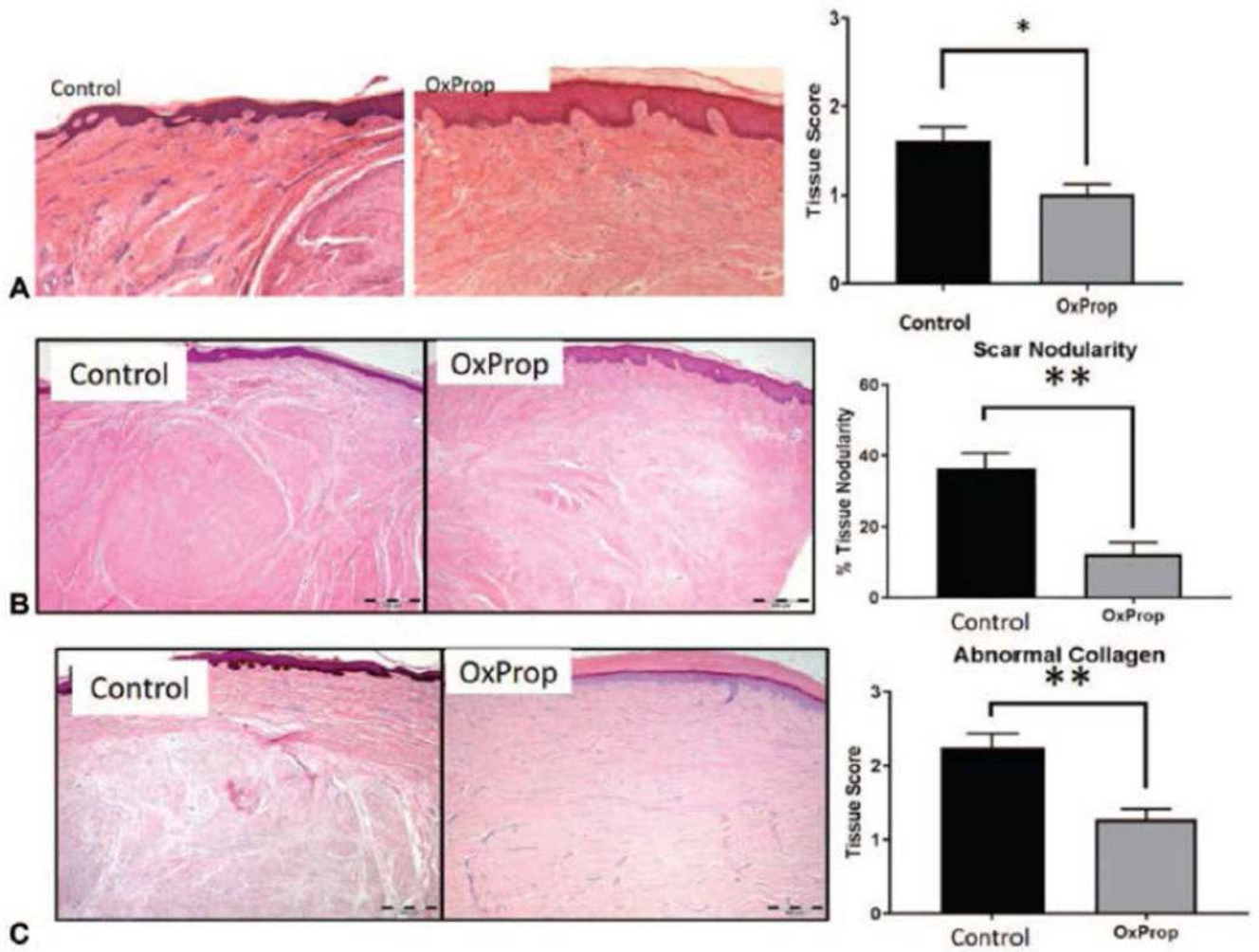


Fig. 4. OxProp significantly reduces dermal inflammation, nodularity and abnormal collagen deposition in postburn scars. (A) Dermal inflammation, (B) nodularity, and (C) abnormal collagen deposition in postburn scars are significantly reduced following OxProp year-long administration compared to control (* $p < 0.05$; ** $p < 0.0001$).

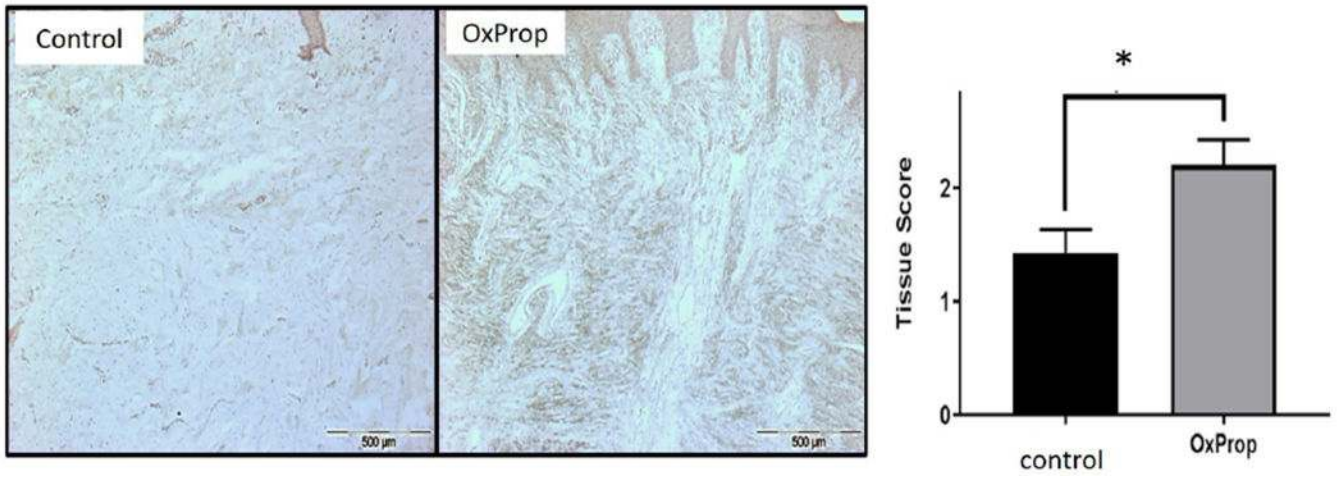


Fig. 5. OxProp increases glucocorticoid receptor expression compared to control. (* $p < 0.0426$).

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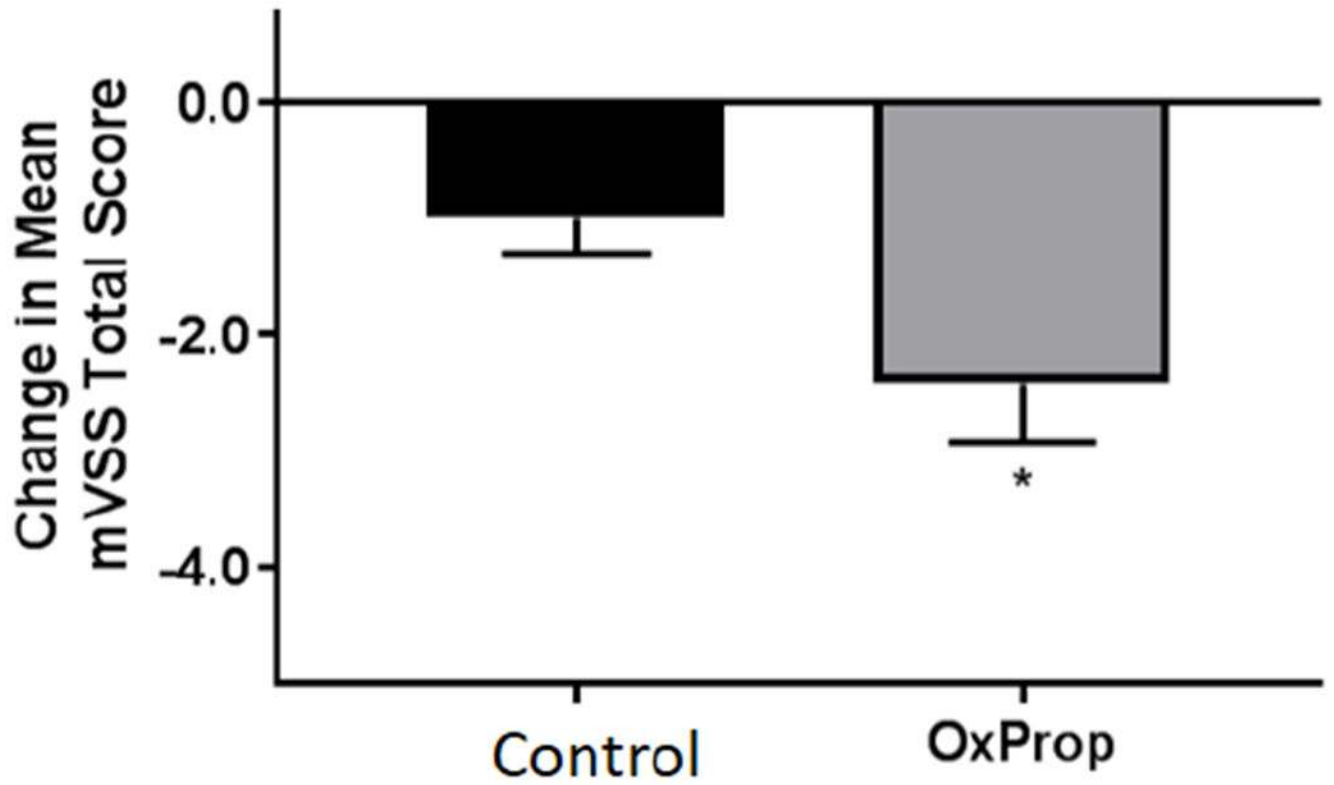


Fig. 6. Severity of postburn hypertrophic scarring is reduced with OxProp following one year treatment. Total mVSS is significantly reduced in OxProp-treated patients between 6 and 12 months following burn injury. * $p < 0.05$.

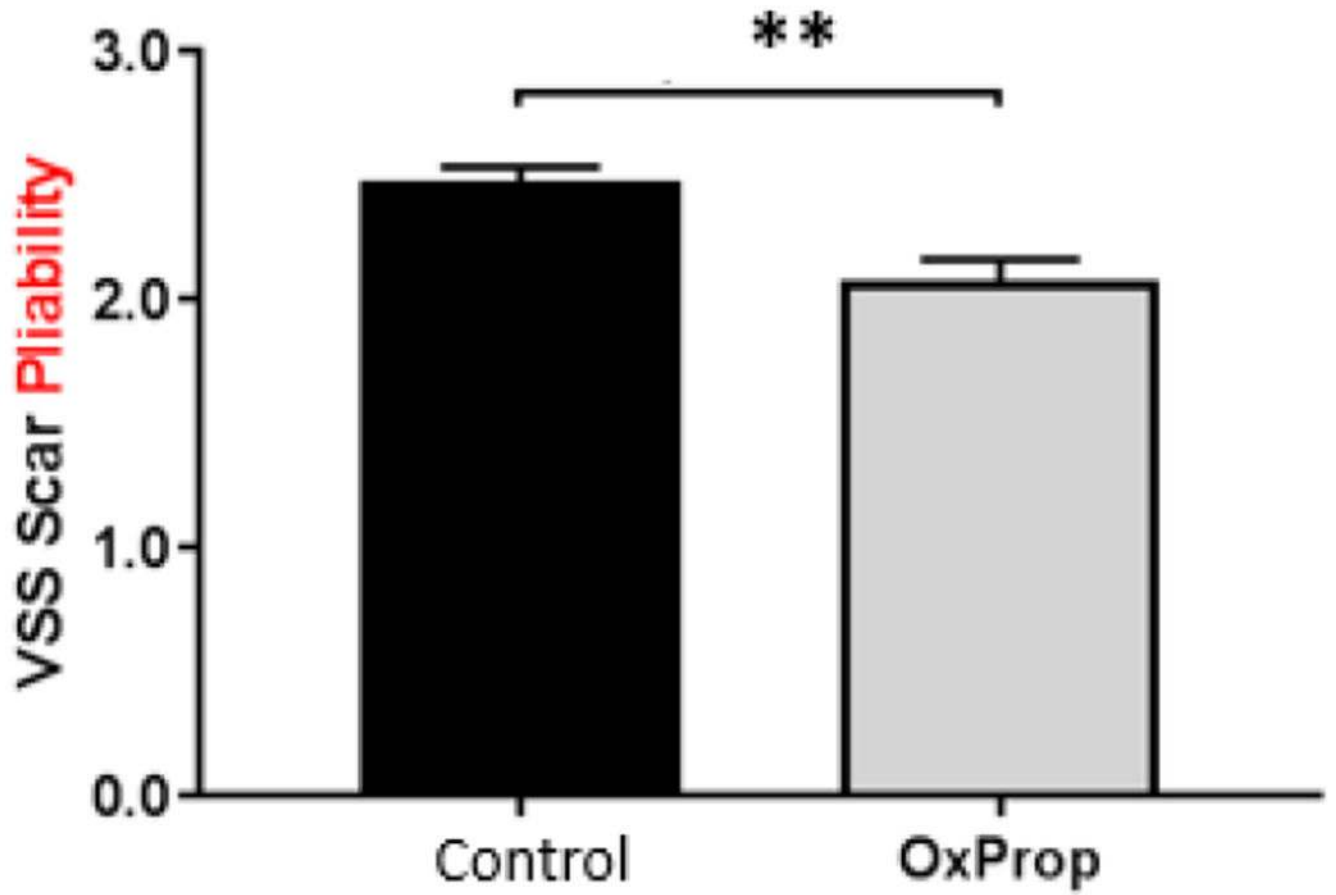


Fig. 7. OxProp makes scar more pliable. Data shown is combined analyses means for all patients over all time points \pm SEM. ** $p < 0.0001$

Table 1.

Demographics

Characteristic	Control (n=226)	OxProp (n=126)
Age (years)	7.1 ± 0.4	7.4 ± 0.5
Sex (% Male)	63	72
Hispanic (%)	94	90
Type of Burn (Scald : Flame : Electrical)	73 : 134 : 19	41 : 70 : 15
TBSA (%)	52 ± 1	50 ± 1
3rd Degree TBSA (%)	37 ± 2	35 ± 2
Delay to Admit (Days, IQR)	3 (2.25)	3 (7.75)
Hospital Length of Stay (Days, IQR)	25 (20.2)	25 (14.75)

Data presented as mean ± standard deviation. IQR, Interquartile Range.

Table 2.

Quality of Life Assessments

Assessment	P	Interpretation	Time Point
How often do you perform leisure activities (movies, sports, restaurants)?	0.007	More activities performed with OxProp	2 years
How often do you accomplish less than you would like because of emotional problems?	0.018	Accomplishing more with OxProp	2 years
In general, would you say your health is excellent, very good, good, fair, or poor?	0.049	Perceived overall health is better with OxProp	2 years
Mental health composite score (based on results of SF12)	0.0012	Perceived mental health is better with OxProp	2 years

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