

Long-Term Administration of Oxandrolone Improves Lung Function in Pediatric Burned Patients

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Pulmonary dysfunction is a significant contributor to morbidity and mortality in the pediatric burned population. We have previously reported that the administration of a synthetic testosterone derivative, oxandrolone, significantly reduced hypermetabolism, and significantly increased height percentile, bone mineral content, lean body mass, and strength in pediatric burned patients. We hypothesize that the administration of oxandrolone will improve pulmonary function in burned pediatric subjects. A subset of severely burned pediatric subjects from a prospective clinical trial ($n = 222$) were included in our study ($n = 54$, 7–18 years, $\geq 30\%$ TBSA burn). The subjects were previously randomized to either the control arm ($n = 35$) or the oxandrolone arm (0.1 mg/kg twice/day for 12 months, $n = 19$). Maximum voluntary ventilation, the ratio between forced expiratory volume and forced vital capacity, and diffusion capacity were measured 6 months following burn injury, and results were compared between burned subjects with and without oxandrolone administration. Maximum expired ventilation (VE_{\max}) was also measured in a subset of burned subjects. Subjects treated with oxandrolone had a significantly higher maximum voluntary ventilation (98 ± 53 L/min vs 115 ± 56 with treatment, $P = .03$). During maximal exercise, subjects treated with oxandrolone had a significantly higher VE_{\max} compared with untreated subjects (32.0 ± 8.7 L/min vs 43.7 ± 13.6 with treatment, $P = .02$). The administration of oxandrolone was associated with improved lung function in pediatric burned patients. (J Burn Care Res 2016;37:273–277)

Annually, approximately 450,000 burn injuries occur in the United States, resulting in 40,000 hospitalizations and 3400 deaths.¹ Nearly 23,000 of these burn patients suffer concomitant lung injury following smoke inhalation.² Inhalation injury significantly

contributes to overall mortality and morbidity in burn patients.^{3,4}

We have previously found that oxandrolone improved patient outcomes in clinical trials from our burn center. Oxandrolone is a synthetic, orally administered, nonaromatizable testosterone derivative that initiates protein synthesis and anabolism via androgen receptors in skeletal muscle. Oxandrolone is preferable to testosterone supplementation because oxandrolone has only 5% of the virilizing activity and lower hepatotoxicity of testosterone. Oxandrolone is an androgenic steroid approved by the Food and Drug Administration to maintain body weight resulting from catabolic states, such as in Turner syndrome, acquired immune deficiency syndrome, major surgery, infections, malnutrition, and neuromuscular diseases.

We have previously shown in severely burned children that long-term administration of oxandrolone for 1 year began during the acute phase of burn injury significantly reduced hypermetabolism.⁵ Oxandrolone also significantly decreased the percentage of predicted resting energy expenditure 6 months post

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injury, increased the height percentile 1 and 2 years post burn, and increased bone mineral content in subjects ages 7 to 18 years 2 to 5 years post burn.⁵ In addition, we showed significantly increased lean body mass in oxandrolone-treated subjects between 7 and 18 years of age who received exercise training when assessed 2 to 5 years post burn. The same subjects (7–18 years) receiving oxandrolone in addition to exercise training had increased strength at 9 to 24 months post burn.⁵

It has been reported that surgical patients with respiratory failure receiving oxandrolone spent significantly more time on a ventilator compared with untreated patients.⁶ Considering that severely burned patients are already prone to pulmonary impairment, we examined subjects treated with oxandrolone for 6 months to assess the effects on lung function. Spirometry and lung volume measurements were performed to test the hypothesis that the administration of oxandrolone would increase pulmonary function in burned patients.

METHODS

Subject Population

Patients 7 to 18 years of age at the time of the burn, with $\geq 30\%$ of TBSA burned, and the need for at least one surgical intervention were included in the study. Exclusion criteria were the decision not to treat due to severity of the burn injury; anoxic brain injury; presence of pre-existing conditions, such as human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis, 5-year history of malignancy, or diabetes; and an inability to obtain informed consent. Administration of oxandrolone was started within 48 hours after the first operation. Oxandrolone was given orally at a dosage of 0.1 mg/kg twice a day for 6 months (BTG Pharmaceuticals, West Conshohocken, PA). This study was part of a larger clinical trial (www.clinicaltrials.gov, NCT00675714) to assess the long-term outcomes of burn survivors following administration of therapeutic agents, such as oxandrolone, propranolol, insulin, and the combination of oxandrolone and propranolol. Informed written consent to a protocol approved by the institutional review board of the University of Texas Medical Branch was obtained from a legal guardian before enrollment in the study. Children older than 7 years assented to participate.

Patient Demographics and Injury Characteristics

Subject age, sex, and TBSA burned were recorded at the time of admission. Age-appropriate diagrams

were used to determine burn size.⁷ Patients received the standard of care in the acute period as previously described.⁵

Pulmonary Function Testing

As part of the long-term assessment of our patients, lung volumes and spirometry were assessed in 54 burned subjects during scheduled outpatient clinic visits 6 months post burn.

The pulmonary function testing (PFT) study variables included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), forced expiratory flow rate between 25–75 of the FVC (FEF_{25-75}), FEV_1/FVC ratio expressed as a percentage ($FEV_1/FVC\%$), total lung capacity, functional residual capacity, carbon monoxide diffusion capacity (DL_{CO}), and maximum voluntary ventilation (MVV). MVV requires a subject to exert significant effort to breathe a maximum volume of air over a 12- to 15-second period. All spirometry measurements were made with a PFT system (Medical Graphics PF/DX, St. Paul, MN) with the subject in an upright position.⁸ Lung volumes were corrected to body temperature and atmospheric pressure. Subjects correctly performed at least two practice forced maximal inhalations and exhalations before any spirometry programs were documented. All expected values were obtained using validated general population equations, and normal predicted values were obtained from Knudson et al.⁹

The procedures were performed in accordance with the guidelines from the American Thoracic Society.¹⁰ The criteria that was used to determine whether the subjects performed the maximal spirometry maneuvers included 1) appropriate curve shape, 2) lack of artifacts in results, such as coughing, premature termination of the test, or delayed onset of measurement, 3) sustained expiration for a minimum of 3 seconds, and 4) performance deemed satisfactory by the tester.⁸

Statistical Analysis

Multiple linear regression models were used to model the relation between the various outcome variables with four predictor variables including treatment group (oxandrolone vs control), sex, age, and percentage of TBSA burned. In addition, TBSA burned, MVV, and DL_{CO} were log-transformed to better approximate a normal distribution. Regression parameter estimates, reverse-transformed as appropriate, were tabulated along with associated 95% confidence intervals and *P* values. The Welch test was used to model higher maximum expired

ventilation (VE_{max}). All statistical tests assumed a 95% level of confidence. Analyses were performed using R statistical software.¹¹

RESULTS

Demographics

A total of 2821 patients were admitted to the Shriners Hospitals for Children-Galveston between 2000 and 2010. Of these patients, 2305 did not meet studies of interventions to attenuate the hypermetabolic response, leaving 516 subjects enrolled in the six arms of the larger clinical trials. Two hundred and twenty-two subjects were included in this analysis of control ($n = 152$) compared with oxandrolone ($n = 70$, 0.1 mg/kg twice a day for 6 months). All patients between the ages of 7 and 18 years with reliable pulmonary function tests in our study were included ($n = 54$, Figure 1) because PFTs are generally considered reliable beginning from the age of 7 years due to the ability to follow specific instructions. The characteristics of the subjects randomized to oxandrolone and control groups were not significantly different (Table 1).

Oxandrolone Improves MVV

Subjects treated with oxandrolone had significantly higher MVV compared with untreated subjects at 6 months post burn (untreated: 98 ± 53 L/min, oxandrolone: 115 ± 56 L/min; $P = .025$). Table 2 shows the model summaries of MVV for the four predictor variables: the treatment groups, sex, age, and TBSA burned. The significant variables include the differences between oxandrolone-treated and untreated groups (factor: 1.327) and age (factor: 1.047). Figure 2 illustrates the 33% increase in MVV in oxandrolone-treated

Table 1. Subject demographics

	Control (n = 35)	Oxandrolone (n = 19)	P
Age (yrs)	13 \pm 3	12 \pm 4	.46
Sex (M:F)	24:11	15:4	.62
Ethnicity (Hispanic, %)	29 (83)	18 (95)	.39
TBSA burned (median)	60 \pm 15 (58)	61 \pm 17 (55)	.97
3rd degree TBSA burned (median)	47 \pm 24 (46)	32 \pm 22 (30)	.06
Inhalation injury (%)	16 (46)	9 (47%)	1.00

subjects compared with untreated subjects. In addition, every 1-year increase in age was associated with a 5% increase in the log of MVV.

Oxandrolone administration had no effect on FEV_1/FVC and DL_{CO} when measured 6 months post burn (FEV_1/FVC : untreated: 1 ± 0 , oxandrolone: 1 ± 0 , $P = .816$; DL_{CO} : untreated: 102 ± 39 , oxandrolone: 111 ± 26 , $P = .684$). Tables 3 and 4 show the model summaries of both pulmonary variables for the four predictor variables.

Exercise Maximal Minute Ventilation Is Higher with Oxandrolone

Twelve control subjects and 12 oxandrolone-treated subjects underwent a maximal exercise treadmill test. There were no statistical differences between their sex, ethnicity, or TBSA burned within the cohorts (Table 5). Subjects treated with oxandrolone had significantly higher VE_{max} compared with untreated subjects 6 months after burn (untreated: 32 ± 9 L/min, oxandrolone: 44 ± 14 L/min, $P = .02$, Figure 3).

DISCUSSION

The pulmonary function changes seen in burned pediatric patients may be caused by a combination of airway and lung inflammation, scar formation, and decreased compliance from chest wall and loss of muscle strength. We have previously reported continued lung dysfunction in the forms of obstructive and/or restrictive disease processes at 2 and 8 years

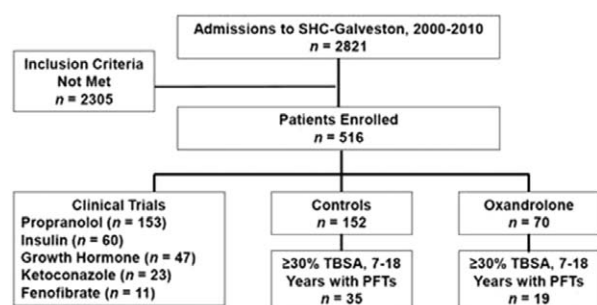


Figure 1. The consort diagram depicts patient allocation into this study. Subjects were included in our analyses if he/she had $\geq 30\%$ TBSA burned, were between the ages of 7 to 18 years, and completed a pulmonary function test at the 6-month time point. PFT, pulmonary function testing; SHC, Shriners Hospitals for Children.

Table 2. Maximum voluntary ventilation

	Factor (95% CI)	P
Oxandrolone/control	1.327 (1.044–1.686)	.025*
Male/female	1.192 (0.918–1.548)	.190
Age	1.047 (1.009–1.086)	.020*
TBSA burned (log)	0.869 (0.532–1.418)	.580

* $P < 0.05$.

CI, confidence interval.

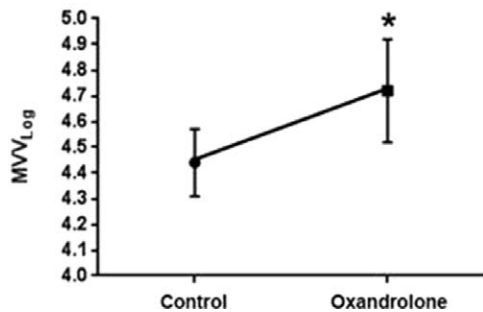


Figure 2. Oxandrolone significantly improves MVV. The means with confidence intervals of MVV between burned subjects with and without oxandrolone treatment are shown. Asterisk represents the significance of $P < .05$ compared with control. MVV, maximum voluntary ventilation.

post burn injury.^{3,12} Previously we suggested that permanent cardiopulmonary impairment was a possible complication in pediatric burn patients,¹³ and we have shown that severely burned children have significantly improved pulmonary function through regular exercise training.¹⁴ In this study, we have shown that subjects treated with oxandrolone had a significantly higher MVV compared with untreated subjects (Figure 2), and that subjects treated with oxandrolone had a significantly higher VE_{max} compared with untreated subjects during maximal exercise (Figure 3).

In a study by Przkora et al¹⁵ of oxandrolone and exercise in pediatric burn patients, it was reported that both the subjects with exercise training and subjects with oxandrolone and exercise training had significantly increased peak oxygen consumption. In addition, in a study of oxandrolone's effects on adult tetraplegia patients, Spungen et al¹⁶ found a significant combined improvement in measures of spirometry. Oxandrolone has been shown to increase net muscle protein synthesis in healthy men¹⁷ and in burned children,¹⁸ which may explain the beneficial effects of oxandrolone on lung physiology.

While studies have shown the benefits of oxandrolone on overall recovery in burn patients, a study by Bulger et al⁶ concluded that ventilator-dependent adult surgical trauma patients treated with oxandrolone spent a significantly longer time on mechanical ventilation. In a response to this, Pereira

Table 4. Diffusion capacity (DL_{CO})

	Factor	Standard Error	P
Oxandrolone/control	0.067	0.160	.684
Male/female	-0.040	0.224	.862
Age	-0.038	0.030	.224
TBSA burned (log)	0.359	0.331	.296

DL_{CO} , carbon monoxide diffusion capacity.

et al¹⁹ discuss the consideration that oxandrolone's blocking of glucocorticoid signaling, lowering of plasma triglycerides, and effects on lipid metabolism decreased surfactant production, a factor that could be accounted for in future implementation.

Spirometry is primarily performed at rest and is largely effort dependent. Previous resting pulmonary function studies have shown degrees of impaired gas exchange and residual pulmonary pathology. However, we did not find differences in the FEV_1/FVC and DL_{CO} between the oxandrolone-treated group and the control group. It is important to note that a maximal exercise treadmill test requires the pulmonary system to perform at a peak level; thus, this test allows the assessment of pulmonary function beyond resting levels. The dynamic measurements of pulmonary function, MVV (Figure 2; $P = .025$) and VE_{max} (Figure 3; $P = .02$), were significantly higher in oxandrolone-treated subjects compared with untreated subjects at 6 months post burn.

We speculate that the administration of oxandrolone may have increased the strength of respiratory accessory muscles. Our results also suggest that lung function should not be looked at simply with static tests, such as the pulmonary function tests, but also with dynamic tests performed during exercise. Future studies will measure the maximum expiratory and inspiratory pressures in our subject population, and will measure pulmonary function 1 year after burn injury. In conclusion, the long-term administration

Table 3. Forced expiratory volume/forced vital capacity

	Adjusted Mean	Standard Error	P
Oxandrolone/control	0.035	0.020	.082
Male/female	-0.044	0.022	.054
Age	0.0001	0.003	.967
TBSA burned (log)	0.058	0.042	.169

Table 5. Demographics of subjects in subset of study with exercise testing

	Control (n = 12)	Oxandrolone (n = 12)	P
Age (yrs)	11 ± 4	13 ± 3	.21
Sex (M:F)	9:3	10:2	1.00
Ethnicity (Hispanic, %)	12 (100)	12 (100)	1.00
TBSA burned (median)	50 ± 8 (48)	59 ± 18 (54)	.15
3rd degree TBSA burned (median)	43 ± 16 (45)	36 ± 19 (32)	.36

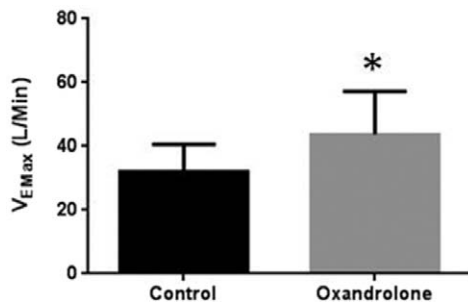


Figure 3. Exercise maximal minute ventilation (VE_{max}) significantly increases with oxandrolone. Means with standard deviations of VE_{max} between burned subjects with and without oxandrolone treatment are shown. Asterisk represents the significance of $P < .05$ compared with control. VE_{max}, maximum expired ventilation

of oxandrolone may be a safe and effective therapy to alleviate lung dysfunction.

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