Published in final edited form as:
J Burn Care Res. 2008 ; 29(6): 902–906. doi:10.1097/BCR.0b013e31818ba14d.

Impact of Oxandrolone Treatment on Acute Outcomes After Severe Burn Injury

Tam N. Pham, MD[*], **Matthew B. Klein, MD**[*], **Nicole S. Gibran, MD**[*], **Brett D. Arnoldo, MD**[†], **Richard L. Gamelli, MD, FACS**[‡], **Geoffrey M. Silver, MD**[‡], **Marc G. Jeschke, MD, PhD**[§], **Celeste C. Finnerty, PhD**[§], **Ronald G. Tompkins, MD, ScD**[‖], and **David N. Herndon, MD**[§]

[*]University of Washington Burn Center, Harborview Medical Center, University of Washington, Seattle

[†]Department of Surgery, Parkland Memorial Hospital, University of Texas Southwestern, Dallas

[‡]Department of Surgery, Loyola University Medical Center, Maywood, Illinois

[§]Department of Surgery, University of Texas Medical Branch and Shriners Hospital, Galveston

[‖]Department of Surgery, Massachusetts General Hospital, Boston

Abstract

Pharmacologic modulation of hypermetabolism clearly benefits children with major burns, however, its role in adult burns remains to be defined. Oxandrolone appears to be a promising anabolic agent although few outcome data are as yet available. We examined whether early oxandrolone treatment in severely burned adults was associated with improved outcomes during acute hospitalization. We evaluated for potential associations between oxandrolone treatment and outcomes in a large cohort of severely burned adults in the context of a multicenter observational study. Patients were dichotomized with respect to oxandrolone treatment, defined as administration within 7 days after admission, with duration of at least 7 days. Acute hospitalization outcomes were compared with univariate and multivariate analyses. One hundred seventeen patients were included in this analysis. Mean patient age was 42.6 years (range, 18–86); 77% were male, with an average TBSA of 44.1%. Baseline and injury characteristics were similar among treatment and nontreatment cohorts. Oxandrolone treatment (N =59) did not impact length of stay but was associated with a lower mortality rate (P = .01) by univariate analysis. Oxandrolone treatment was independently associated with higher survival by adjusted analyses (P = .02). Examination of early oxandrolone treatment in this cohort of severely burned adults suggests that this therapy is safe and may be associated with improved survival. Further studies are necessary to define the exact mechanisms by which oxandrolone is beneficial during inpatient treatment.

The hypermetabolic response to injury remains an enormous challenge in the management of severely burned patients. Major burn injuries are associated with development of fever, tachycardia, excessive protein catabolism, and severe weight loss. This response has been shown to last up to 1 year, impacting both acute recovery and rehabilitation.[1] Although adequate fluid resuscitation, prompt surgical excision and grafting of the burn wound remain

Address correspondence to Tam N. Pham, MD, University of Washington Burn Center, Harborview Medical Center, Box 359796, 325 Ninth Avenue, Seattle, Washington 98104.

This Manuscript was prepared using a dataset obtained from the Glue Grant program and does not necessarily reflect the opinions or views of the Inflammation and the Host Response to Injury Investigators or the NIGMS

the cornerstones of modern burn care, recent evidence suggests that pharmacologic modulation of the hypermetabolic response may improve outcomes after burn injury.[2–4]

Anabolic agents have emerged as potential agents to improve net protein balance and preserve lean-body mass in severely burned patients.[5–7] Oxandrolone, a testosterone analog with weak virilizing potential, has been evaluated in both children and adults with severe burns. In the acute phase of illness, children treated with oxandrolone had improved net protein balance, lean body mass and liver protein synthesis.[8] During the rehabilitative phase, oxandrolone also demonstrated sustained benefits in lean body mass, growth recovery, and bone mineral content beyond at one year and beyond.[9,10] Alternatively, data on beneficial effects in adults are more limited. A recent randomized trial demonstrated that oxandrolone treatment was associated with decreased hospital length of stay,[11] but did not significantly influence other acute hospital outcomes. Oxandrolone is still not considered standard treatment for adults after burn injury, likely due to the paucity of data on the beneficial effects. The purpose of this study was to examine the effects of oxandrolone in a cohort of severely burned patients enrolled in the National Institutes of Health funded “Inflammation and Host Response to Injury” study.[12]

Methods

Study Overview

We evaluated the association between oxandrolone treatment and acute hospitalization outcomes in a large cohort of severely burned patients in the context of a multicenter observational study, the Inflammation and Host Response to Injury Study. The primary intent of this collaborative program is to define proteomic and genomic basis of injury responses. As part of the study, a large clinical database has been collected with detailed information on patient and injury characteristics and outcomes. This analysis was a secondary use of the database.

Patients—Criteria for enrollment in the burn component of the Inflammation and Host Response to Injury study included burn surface-area ≥20%TBSA without concomitant trauma injury, intent to treat and admission within 96 hours of injury. Participating burn centers were located at Massachusetts General Hospital (Boston, MA), Loyola University Medical Center (Maywood, IL), The University of Texas Medical Branch (Galveston, TX), The University of Texas-Southwestern (Dallas, TX), and Harborview Medical Center (Seattle, WA). The overall multicenter study was performed after approval of the Institutional Review Boards of the respective institutions. Access to the deidentified database for this project was performed after permission was granted by the Inflammation and Host Response to Injury Core Committee and following approval of the University of Washington Institutional Review Board.

Data Collection—Trained nurse abstractors at each site prospectively entered clinical data into a web-based data collection platform. Core staff-members evaluated data integrity for internal consistency. An independent physician and chart abstractor audited a random sample of charts for data for data consistency. For this study, we abstracted data on all enrolled adult patients with complete hospitalization entries, including inpatient medication administration.

Treatment Definitions—No standard operating procedures were established for the use of oxandrolone in the overall project.[13] Thus, the decision to treat with oxandrolone was left to the attending surgeon at each center. For the purpose of this study, we defined treated subjects as patients initiated on oxandrolone within 7 days of admission and maintained on

the same treatment for at least 7 days. Patients who received treatment for fewer than 7 days were categorized as nontreated.

Data Analysis—Baseline patient and injury characteristics collected for analysis included age, gender, %TBSA, presence of inhalation injury and admission APACHE II scores. Diagnosis of inhalation injury was determined by the standard practice of the participating institution (either by clinical history/physical examination or bronchoscopy). Outcomes included intensive care unit length of stay, overall hospital length of stay, infectious complications, development of late multiple organ dysfunction and mortality. Nosocomial infections were defined as infections diagnosed after 72 hours of hospitalization. [13] Late-onset Multiple Organ Dysfunction Syndrome (MODS) was defined as a maximum Denver score ≥4 (Table 1)[14] after day 7 of hospitalization. All prior episodes of organ dysfunction were likely not influenced by oxandrolone treatment and therefore were excluded from analysis. Given the potential liver toxicity of oxandrolone, we compared the incidence of liver dysfunction between treated and untreated patients, defined as serum bilirubin ≥2.0 mg/dl during hospitalization.

Means and SD were calculated for all appropriate variables. Differences between groups were calculated by Chi-squared or Fisher's exact test for categorical variables and by Wilcoxon rank-sum test for continuous variables. Subjects who died before discharge were excluded from the calculations of lengths of stay. Logistic regression was performed to adjust for patient and injury characteristics that could confound the relationship between oxandrolone administration and outcome. Significance was accepted at $P \leq .05$.

Results

A total of 117 adult burn patients had complete data sets at the time of this study. Baseline patient and injury characteristics are summarized in Table 2. Mean subject age was 42.6 years (SD, 16.1; range, 18–86). Most subjects were male, with a flame or flash-flame as the most common mechanism of injury and 48% of patients had an inhalation injury diagnosis. A total of 59 (50%) patients met criteria for oxandrolone treatment. Patient and injury characteristics were similar between treatment and nontreatment cohorts, except that patients treated with oxandrolone had a higher mean percent full-thickness injury (32.8 vs 27.9%, $P = .12$, Table 2). Mean duration of oxandrolone treatment was 42.9 days (SD, 36.0; range, 7–180 days).

Mean numbers of operations, ventilator days, intensive care length of stay, hospital length of stay, and nosocomial infections were similar between those patients who received oxandrolone and those who did not (Table 3). The incidence of MODS was lower in patients who received oxandrolone therapy (10.2 vs 20.6%, $P = .11$). Overall mortality rate was significantly lower in the treatment group (10.2 vs 27.6%, $P = .01$). Four patients treated with oxandrolone developed liver dysfunction compared with eight patients in the nontreated group ($P = .22$).

To control for the potential confounders of the relationship between oxandrolone administration and development of MODS and mortality, multivariate logistic regression analyses were performed for each outcome. In adjusted analyses, there was no significant association between oxandrolone and decreased likelihood of developing MODS (OR, 0.6; $P= .50$; 95% CI, 0.17–2.42). However, oxandrolone treatment was independently associated with decreased mortality (OR, 0.1; $P = .02$; 95% CI, 0.02– 0.70) (Table 4).

Discussion

Modulation of the hypermetabolic response remains an enormous challenge in the treatment of burn patients. In this study of oxandrolone effects on acute outcomes in severely burned adult patients, we found that treatment with oxandrolone was safe and independently associated with improved survival.

Substantial data support the use of oxandrolone during acute hospitalization in severely burned children, in whom oxandrolone improves hepatic constitutive protein synthesis, helps preserve lean body mass, and reduces length of hospitalization.[15,16] Furthermore, combining oxandrolone with an exercise program up to 1 year after injury improves lean body mass and muscle strength during rehabilitation. [9,17] Data on the beneficial effects of oxandrolone administered to adults during the acute postinjury phase and rehabilitative phase are more limited. Demling and Orgill reported significantly accelerated donor site healing when oxandrolone was administered early after injury (days 2–3).[18] In addition, Demling and DeSanti examined the benefits of oxandrolone administered to adults in the recovery phase and has reported significant improvements in lean body mass, muscle strength and endurance with prolonged oxandrolone treatment.[2,19,20] The American Burn Association Multicenter Trials Group examined the potential benefits of oxandrolone treatment beginning at 5 days postburn in a multicenter prospective randomized, placebo-controlled trial.[11] The study's main findings were that oxandrolone treatment was safe and associated with a shortened length of hospitalization (31.6 days vs 43.3 days, $P < .05$). Hospital complications were listed in each group, but were relatively uncommon. MODS and mortality incidences were not specifically examined.

The purpose of our study was to examine the effect of oxandrolone treatment on a number of additional clinical outcomes collected as part of a large-scale National Institutes of Health multicenter collaborative study. We found that early oxandrolone treatment was independently associated with higher survival. Since oxandrolone treatment did not appear to impact other measured outcomes, these findings do not clarify by which means oxandrolone may derive its potential benefit. In fact, the weak association found between oxandrolone and a lower incidence of MODS on univariate was negated when adjusting for known confounding factors. Therefore, differences in the incidence of MODS cannot be used to explain the association between oxandrolone exposure and a lower mortality rate. In contrast to the Multicenter Trial Group's findings, we did not observe any difference in length of stay between treated and untreated groups. There are admittedly many different factors other than donor site healing and recovery time that can impact length of stay. These may include available medical and rehabilitation resources near a patient's home, transportation and follow-up issues, and patients' financial resources. These factors especially influence the timing of discharge at regional burn centers.

In addition to its effectiveness, the safety of oxandrolone is another critical concern surrounding its routine use. Much has been written about the association between anabolic steroids and liver dysfunction.[11,19,21] Both Demling and Wolf documented increases in liver enzyme levels with oxandrolone treatment, but none of the patients in their studies went on to develop clinically significant dysfunction. The incidence of hepatic dysfunction in our study was actually lower in patients treated with oxandrolone. In fact, oxandrolone has been successfully tested in patients with established alcoholic liver dysfunction as an adjunct to aggressive nutritional support.[22,23] Furthermore, we did not document any adverse impact of oxandrolone on any other measured outcome. Taken altogether, our results corroborate the overall safety of this medication in burn patients.[9,15,21]

There are several limitations to consider in this study. First and foremost, the administration of oxandrolone was not protocolized. Rather, the decision to initiate oxandrolone treatment was left to treating physicians at the individual centers. Second, despite the multicenter nature of this study, only 117 subjects had complete data at the time of this analysis. This relatively small number is the likely reason for the wide range of confidence intervals in the multivariate analyses.

Treatment groups had to be carefully defined in this retrospective cohort analysis in order to limit bias. We screened the database and noted that all deaths occurred after 1 week (range, 8–74 days). Therefore, we chose to define treated subjects as having received oxandrolone by day 7 to avoid selecting for nonsurvivors into the untreated cohort. If 7-day treatment duration were the sole criterion to define oxandrolone treatment, the association between oxandrolone and MODS would become significant in multivariate regression. This association however, would suffer from the bias of adding surviving patients initiated on oxandrolone much later in their hospital course. Admittedly, there is no standard with respect to the timing of oxandrolone treatment. Investigators at the Galveston Shriners Hospitals for Children have initiated treatment after the patient's second surgical procedure, usually at day 6 to 10.[8,15] In adult burn patients, Demling and DeSanti have trialed oxandrolone both in the acute phase (day 7–10) and in the rehabilitation phase.[2,19,20] More recently, the burn multicenter trial group randomized patients to either oxandrolone or placebo at day 5 after injury.[11]

In conclusion, early administration of oxandrolone was independently associated with higher survival in this retrospective analysis. Along with previous reports in both children and adults, several lines of evidence now suggest a benefit to oxandrolone treatment in the acute management of severely burned patients. These data warrant confirmation in a rigorous, large scale prospective randomized trial before we can consider oxandrolone treatment a standard. This trial should include careful measurements of metabolic and nutritional parameters, as they may clarify potential beneficial effects of oxandrolone in adult burn patients.

Acknowledgments

The investigators acknowledge the contribution of the Inflammation and the Host Response to Injury Large-Scale Collaborative Project Award 2-U54-GM062119 from the National Institute of General Medical Sciences.

The Inflammation and the Host Response to Injury “Glue Grant” program is supported by the National Institute of General Medical Sciences

References

1. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. Lancet. 2004; 363:1895–902. [PubMed: 15183630]
2. Demling RH, DeSanti L. Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. J Trauma. 1997; 43:47–51. [PubMed: 9253907]
3. Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. Ann Surg. 1988; 208:484–92. [PubMed: 3052328]
4. Pham TN, Gibran NS. Thermal and electrical injuries. Surg Clin North Am. 2007; 87:185–206. [PubMed: 17127128]
5. Ferrando AA, Sheffield-Moore M, Wolf SE, Herndon DN, Wolfe RR. Testosterone administration in severe burns ameliorates muscle catabolism. Crit Care Med. 2001; 29:1936–42. [PubMed: 11588456]

6. Sakurai Y, Aarsland A, Herndon DN, et al. Stimulation of muscle protein synthesis by long-term insulin infusion in severely burned patients. Ann Surg. 1995; 222:283–94. [PubMed: 7677459]
7. Solomon V, Madihally S, Mitchell RN, Yarmush M, Toner M. Antiproteolytic action of insulin in burn-injured rats. J Surg Res. 2002; 105:234–42. [PubMed: 12121712]
8. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. Ann Surg. 2001; 233:556–64. [PubMed: 11303139]
9. Przkora R, Jeschke MG, Barrow RE, et al. Metabolic and hormonal changes of severely burned children receiving long-term oxandrolone treatment. Ann Surg. 2005; 242:384–9. [PubMed: 16135924]
10. Murphy KD, Thomas S, Mlcak RP, Chinkes DL, Klein GL, Herndon DN. Effects of long-term oxandrolone administration in severely burned children. Surgery. 2004; 136:219–24. [PubMed: 15300183]
11. Wolf SE, Edelman LS, Kemalyan N, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. J Burn Care Res. 2006; 27:131–9. [PubMed: 16566555]
12. Klein MB, Silver G, Gamelli RL, et al. Inflammation and the host response to injury: an overview of the multicenter study of the genomic and proteomic response to burn injury. J Burn Care Res. 2006; 27:448–51. [PubMed: 16819346]
13. Silver GM, Klein MB, Herndon DN, et al. Standard operating procedures for the clinical management of patients enrolled in a prospective study of inflammation and the host response to thermal injury. J Burn Care Res. 2007; 28:222–30. [PubMed: 17351437]
14. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. The role of the lung in postinjury multiple organ failure. Surgery. 2005; 138:749–57. [PubMed: 16269305]
15. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. Ann Surg. 2007; 246:351–62. [PubMed: 17717439]
16. Thomas S, Wolf SE, Murphy KD, Chinkes DL, Herndon DN. The long-term effect of oxandrolone on hepatic acute phase proteins in severely burned children. J Trauma. 2004; 56:37–44. [PubMed: 14749563]
17. Przkora R, Herndon DN, Suman OE. The effects of oxandrolone and exercise on muscle mass and function in children with severe burns. Pediatrics. 2007; 119:109–16. [PubMed: 17200277]
18. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. J Crit Care. 2000; 15:12–17. [PubMed: 10757193]
19. Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. Burns. 2001; 27:46–51. [PubMed: 11164665]
20. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003; 29:793–7. [PubMed: 14636753]
21. McCullough MC, Namias N, Schulman C, et al. Incidence of hepatic dysfunction is equivalent in burn patients receiving oxandrolone and controls. J Burn Care Res. 2007; 28:412–20. [PubMed: 17438485]
22. Bonkovsky HL, Singh RH, Jafri IH, et al. A randomized, controlled trial of treatment of alcoholic hepatitis with parenteral nutrition and oxandrolone. II. Short-term effects on nitrogen metabolism, metabolic balance, and nutrition. Am J Gastroenterol. 1991; 86:1209–18. [PubMed: 1909086]
23. Mendenhall CL, Moritz TE, Roselle GA, et al. The VA Cooperative Study Group #275. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. JPEN J Parenter Enteral Nutr. 1995; 19:258–65. [PubMed: 8523623]

Table 1

Denver postinjury multiple organ dysfunction score*[14]

Organ System Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary: PaO_2/FiO_2	>250	201–250	101–200	≤100
Renal: Creatinine (mg/dl)	≤1.8	1.9–2.5	2.6–5.0	>5.0
Hepatic: Total bilirubin (mg/dl)	≤2.0	2.1–4.0	4.1–8.0	>8.0
Cardiovascular	No inotropes and cardiac index >3.0	Minimal inotropes and CI <3.0	Moderate inotropes	High inotropes

* The sum of grades from each component are added to determine total score.

Table 2

Patient and injury characteristics, by oxandrolone treatment*

Oxandrolone	Treated (n = 59)	Nontreated (n = 58)	*P*
Age	42.3 (±14.1)	42.9 (±18.1)	.73
%Male	78	75	.70
BMI	26.5 (±6.5)	27.4 (±6.1)	.28
%TBSA	42.9 (±16.9)	46.3 (±20.3)	.45
%Full-thickness	32.8 (±18.3)	27.9 (±19.6)	.12
%Inhalation injury	52	43	.30
Apache II score	22.2 (±8.6)	21.7 (±8.8)	.73

*Data presented as mean (±SD) or percentage.

Table 3

Hospital outcomes, by oxandrolone treatment*

Oxandrolone	Treated (n = 59)	Nontreated (n = 58)	*P*
Oxandrolone treatment length	42.9 (±36.0)	N/A	N/A
Operations	6.3 (±4.5)	5.1 (±4.3)	.36
Units transfused	10.9 (±13.4)	13.7 (±21.9)	.93
Ventilator days	25.8 (±32.6)	21.8 (±21.2)	.75
LOS/TBSA†	1.5 (±1.0)	1.1 (±6.2)	.25
LOS/Full-thickness injury†	3.0 (±5.4)	4.6 (±7.4)	.31
ICU LOS†	48.3 (±45.7)	36.4 (±34.1)	.26
Nosocomial infection	76	83	.38
Multiple organ dysfunction (MODS)	10.2	20.7	.11
Mortality	10.2	27.6	.01

LOS, length of stay.

*Data presented as mean (±SD) or percentage.

†Length of stay calculations on survivors only.

Table 4
Adjusted analyses for MODS and mortality

Variable	Adjusted Odds Ratio	*P*	95% CI*
MODS			
Oxandrolone treatment	0.6	.50	0.17–2.42
Age	1.1	.02	1.02–1.11
%TBSA	1.1	<.01	1.03–1.11
%Full-thickness	1.0	.68	0.97–1.04
Inhalation injury	1.4	.64	0.37–5.02
Mortality			
Oxandrolone treatment	0.1	.02	0.02–0.70
Age	1.1	<.01	1.04–1.16
%TBSA	1.1	<.01	1.03–1.11
%Full-thickness	1.1	<.01	1.03–1.14
Inhalation injury	1.0	.96	0.21–5.14

* Denotes 95% confidence interval.