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Oxandrolone in trauma patients

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Abstract

Study Objective
To determine the effect of oxandrolone administration on nutritional and clinical outcomes after multiple trauma.

Design
Prospective, randomized, double-blind, placebo-controlled study. Setting. Level 1 trauma center in a university teaching hospital.

Patients
Sixty-two patients requiring enteral nutrition, 60 of whom completed the study.

Intervention
Patients were randomized to receive either oxandrolone 10 mg or placebo twice/day for a maximum of 28 days.

Measurements and Main Results
Total urinary nitrogen, prealbumin, nitrogen balance, total body water, and body cell mass were measured on day 1 of enteral nutrition and then at day 7, day 10, and study exit. Patients were assessed daily for metabolic and infectious complications. The two groups were similar for demographics and dosage of enteral nutrition. Measurement of total urinary nitrogen at study entry showed both groups to be highly catabolic (oxandrolone 17.2 ± 4.9, placebo 19.1 ± 10.8 g/day, NS). On days 7 and 10, total urinary nitrogen increased in both groups; however, there was no significant difference between groups. Nitrogen balance was negative throughout the study in each group. Body cell mass decreased slightly in both groups over the study period. Prealbumin serum concentrations increased significantly in both groups at day 10 and study exit compared with study entry. The groups did not differ significantly for length of hospital stay (oxandrolone 30.8 ± 17.9, placebo 27.0 ± 25.7 days), length of intensive care unit stay (oxandrolone 17.1 ± 7.8, placebo 15.5 ± 9.7 days), and frequency of pneumonia or sepsis (oxandrolone 48, placebo 43 episodes).

Conclusion
Oxandrolone 20 mg/day does not have obvious benefit in nutritional and clinical outcomes during the first month after multiple trauma.

The catabolic response to injury is associated with elevated glucocorticoid, catecholamine, and glucagon serum concentrations and a breakdown of body protein. Critical injury causes hypermetabolism and hypercatabolism, resulting in an increase in resting energy expenditure and decrease in body cell mass.[1] Patients sustaining major trauma had a mean body protein loss of 1.62 kg (16%) over 21 days, with skeletal muscle accounting for the largest percentage.[1] Specialized nutrition support (parenteral, enteral) is given to these patients to minimize this protein loss. Quantities as high as 2–3 g/kg/day of protein have been administered in attempts to produce net anabolism.[2] Although specialized nutrition support improves the quality of patient care, it fails to ameliorate net protein catabolism.[3] Anabolic agents have been investigated for their use in preserving body cell mass and improving muscle strength. Studies in trauma and thermally injured patients reported improved nitrogen retention and restored muscle mass, but therapy was limited by androgenic complications.[4,5]

Oxandrolone is a testosterone analog with reported anabolic activity 5–10 times that of older anabolic agents and with considerably fewer androgenic effects. It improved body cell mass in thermally injured patients during the recovery phase[6] and restored muscle mass in patients with acquired immunodeficiency syndrome.[7,8] To our knowledge, no study has investigated oxandrolone during the acute phase of injury in trauma patients. We examined the agent's effects on nutritional and clinical outcomes after multiple trauma.

Methods

This was a prospective, double-blinded, randomized, placebo-controlled study conducted in a level 1 trauma center. It was approved by a university investigational review board and the hospital. Written informed consent was obtained from all patients. A total of 62 patients with multiple trauma requiring enteral nutrition were randomized by a table of random numbers to receive either oxandrolone (Oxandren; BTG Corporation, Iselin, NJ) 10 mg twice/day (maximum approved dosage for catabolic patients) or placebo. Patients had to be 18–60 years of age, have sustained multiple trauma, and require enteral nutrition. Those who were less than 90% of ideal body weight were considered undernourished and those more than 30% of ideal body weight were considered obese. Exclusion criteria were renal insufficiency or failure defined by a serum creatinine concentration above 2 mg/dl; hepatic insufficiency defined by a total bilirubin concentration above 3 mg/dl, or cirrhosis by history or biopsy; gastrointestinal malabsorptive disorders, metastatic carcinoma, diabetes mellitus, or human immunovirus (HIV) infection; hypersensitivity to anabolic steroids; and pregnancy.

Injury Severity[9] and Trauma[10] scores were calculated at hospital admission. Acute Physiology and Chronic Health Evaluation II (APACHE II)[11] and Glascow Coma Scale[12] scores were calculated for each patient within the first 24 hours of entering the study. Study entry occurred within the first five days after trauma.

Patients received oxandrolone or placebo for 28 days unless they were discharged or transferred to another facility, in which case the drug was discontinued. Oxandrolone tablets or placebo

tablets (thiamine 50 mg) were crushed and suspended in water before administration through a nasogastric feeding tube or enterostomy. Patients received tablets orally when they were able to consume an oral diet. Compliance with therapy was recorded every day.

Enteral nutrition was administered to each group as an immune-enhancing formula (ImmunAid; McGaw Laboratories, Santa Ana, CA) to provide 30 total calories/kg/day and 2.4 g protein/kg/day while in the intensive care unit (ICU). All patients who were transferred out of the ICU were changed to a polymeric, high-protein, fiber-containing enteral formula. Oral diets were prescribed as appropriate, and enteral nutrition was discontinued when patients were able to consume more than 50% of required calories orally. Patients were monitored daily by the nutrition support service for metabolic, gastrointestinal, pulmonary, and mechanical complications. Mean daily and mean maximum caloric and protein intake were calculated for each group.

Plasma electrolytes (Na^+, K^+, Cl^-, total CO_2, Ca^{2+}, Mg^{2+}, PO_4^{3-}), blood urea nitrogen (BUN), creatinine, prealbumin, albumin, aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase were measured at study admission and days 7, 10, and 28, or study exit if before day 28. Twenty-four-hour urine samples were collected at study admission and days 7, 10, and 28 or study exit for total urinary nitrogen (TUN). A 10-ml aliquot was obtained from the 24-hour urine collection and immediately frozen at -20°C. Total urinary nitrogen was determined by pyrochemilumenescence.

Total body water, lean body mass, and body cell mass were calculated by bioelectrical impedance analysis on the same schedule. Computerized Bioelectrical Analyzer System (RJL System, Inc., Detroit, MI) was used as described previously.[13,14]

Clinical outcome variables including length of ICU stay, hospital stay, and mechanical ventilation days were recorded. Patients were assessed daily for infectious complications. Infections were determined based on set criteria and defined as pneumonia by bronchial alveolar lavage with 10^5 or more colony-forming units/ml[15]; sepsis, severe sepsis, septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and systemic inflammatory response syndrome (SIRS) by the American College of Chest Physicians–Society of Critical Care Medicine consensus statement[16]; abdominal infections including intraabdominal abscess, necrotizing fasciitis, and peritonitis by positive abdominal infection and physical diagnosis; and sinusitis by mucosal thickening, computerized tomographic scan, and positive cultures. Infections were verified and documented by a trauma surgical physician who was blinded to study therapy.

Statistical Analysis

A sample of 30 in each group was estimated to observe a decrease in TUN of 20% from baseline to day 7 of the study in patients receiving oxandrolone, with β of 0.8 and α of 0.05. Continuous data were analyzed by analysis of variance (ANOVA) with Tukey's test for post hoc pairwise

Table 1. Summary of Group Demographics

	Oxandrolone (n=30)	Placebo (n=30)
Age (yrs)	33.9 ± 12.5	35.2 ± 11.0
M/F	26/4	29/1
Height (cm)	177.3 ± 6.4	179.1 ± 9.6
Weight (kg)	83.2 ± 19.4	83.0 ± 18.7
Ideal body weight (%)	112 ± 22	110 ± 19
APACHE II score	15.8 ± 5.8	15.5 ± 5.5
Injury Severity score	27.8 ± 11.3	25.1 ± 13.5
Trauma score	8.2 ± 3.5	7.8 ± 3.4
Glasgow Coma Scale score	8.9 ± 5.2	8.3 ± 4.9
Trauma (blunt/penetrating)	24/6	19/11

Values are expressed as mean ± SD.

comparisons. Categoric data were analyzed by x^2 test or Fisher's exact test. A p value less than 0.05 was considered statistically significant. All data are expressed as mean ± standard deviation (SD).

Results

Sixty-two patients were enrolled. Two who were receiving placebo withdrew, leaving 60 patients with 30 in each group. One patient withdrew because he believed reinstitution of mechanical ventilation was associated with the study. The other patient did not provide a reason for withdrawal. The two groups were similar for demographics (Table 1) and administration of specialized nutrition support (Table 2). Using admission weight and height, the oxandrolone group consisted of 22 normally nourished, 6 obese, and 2 undernourished patients. The placebo group had 22 normally nourished, 5 obese, 3 undernourished patients. All patients were entered in the study within 1–5 days after injury.

No statistically significant differences were observed in the number of study days between the oxandrolone and placebo group (20.3 ± 8.8 vs 18.1 ± 8.2 days, NS), and each group received over 90% of prescribed doses of oxandrolone or placebo. In the oxandrolone group, 22 patients were fed by small-bore nasogastric feeding tube, 2 by nasojejunal tube, 5 by jejunostomy tube, and 1 by gastrostomy tube. Respective figures in the placebo group were 25, 1, 3, and 1. Eight patients in the oxandrolone group and four in the placebo group required parenteral nutrition for an average of 8 and 9 days, respectively, secondary to gastrointestinal intolerance to tube feedings. The decision to start parenteral nutrition was made jointly between nutrition support and trauma teams. Parenteral nutrition consisted of a formulation that was isonitrogenous and isocaloric to the immune-enhancing enteral formula. During parenteral nutrition, oxandrolone or placebo was given through a nasogastric tube that was clamped for 1 hour after each administration.

Six patients in the oxandrolone group and five in the placebo group received propofol for sedation or anxiety. Fat calories from propofol were calculated, and no significant differences

Table 2. Nutrition Support Administration

	Oxandralone	Placebo
Length of specialized nutrition support (days)	20.0 ± 8.7	17.4 ± 9.3
Length of enteral nutrition support (days)	16.4 ± 8.8	14.6 ± 9.3
Maximum calories received in 1 day (kcal/kg/day)	29.9 ± 10.4	27.4 ± 8.6
Maximum protein received in 1 day (g protein/kg/day)	2.2 ± 0.7	2.1 ± 0.7
Nitrogen intake (g/day)		
Day 1	7.9 ± 6.2	8.4 ± 5.8
Day 7	16.5 ± 10.1	20.6 ± 8.8
Day 10	16.8 ± 12.6	18.6 ± 10.8
Day 28 or study exit	16.0 ± 4.8	12.9 ± 10.7
Total urinary nitrogen excretion (g/day)		
Day 1	17.2 ± 4.8	19.1 ± 10.8
Day 7	22.2 ± 11.2	28.0 ± 15.5
Day 10	26.0 ± 11.9	27.1 ± 5.9
Day 28 or study exit	16.5 ± 7.6	18.3 ± 10.9
Nitrogen balance (g/day)		
Day 1	-11.4 ± 7.6	-12.8 ± 11.8
Day 7	-9.5 ± 10.8	-10.9 ± 20.8
Day 10	-11.8 ± 9.3	-15.1 ± 19.3
Day 28 or study exit	-3.8 ± 10.6	-6.3 ± 12.5
Received parenteral nutrition (no.)	8	4

Values are expressed as mean ± SD.

Table 3. Serum Protein Concentrations and Selected Chemistries

	Oxandrolone	Placebo
Serum prelbumin concentration (mg/dl)		
Day 1	11.6 ± 3.9	10.1 ± 3.0
Day 7	14.8 ± 6.2	14.1 ± 7.0
Day 10	20.9 ± 13.0[a]	15.8 ± 7.9[a]
Day 28 or study exit	30.5 ± 12.7[a,b]	23.0 ± 7.3[a]
Serum albumin concentration (g/dl)		
Day 1	2.3 ± 0.6	2.2 ± 0.6
Day 7	2.0 ± 0.5	2.2 ± 0.8
Day 10	2.1 ± 0.6	2.3 ± 1.1
Day 28 or study exit	2.5 ± 0.6	2.6 ± 0.6
Serum glucose concentration (mg/dl)		
Day 1	119 ± 24	133 ± 30
Day 28 or study exit	116 ± 37	116 ± 25
Blood urea nitrogen (mg/dl)		
Day 1	12.4 ± 5.3	13.9 ± 8.9
Day 7	20.3 ± 14.5	23.4 ± 14.6
Day 10	28.9 ± 28	27.7 ± 23.2
Day 28 or study exit	28.5 ± 40.8	24.5 ± 18.3
Serum creatinine (mg/dl)		
Day 1	0.9 ± 0.3	0.9 ± 0.2
Day 7	0.9 ± 0.5	0.9 ± 0.2
Day 10	1.1 ± 1.3	0.9 ± 0.4
Day 28 or study exit	1.0 ± 1.0	0.9 ± 0.8

Data are expressed as mean ± SD.
[a] $p < 0.05$ compared with day 1 concentrations.
[b] $p < 0.05$ between groups.

were observed between patients receiving this drug in the two groups (672 ± 358 vs 674 ± 304 calories/day, NS).

Measurement of TUN at study entry showed both groups to be highly catabolic. On days 7 and 10, TUN increased in both groups. Mean TUN decreased by day 28 or study exit. Mean nitrogen balance was negative on all study days in both groups. No statistically significant difference between groups was seen for any of these values.

Prealbumin serum concentrations increased significantly in both groups at days 10 and study exit compared with study entry (Table 3). The only significant difference between groups was noted at study exit. No significant differences were appreciated with serum albumin concentrations or serum glucose concentrations within or between groups. There were no significant differences between groups in BUN and serum creatinine concentration. Mean BUN concentrations approximately doubled in each group from study entrance to exit. Hepatic chemistry values in the two groups were total bilirubin concentration (day 1, 0.9 ± 0.7 oxandrolone, 1.0 ± 0.8 g/dl placebo; exit, 0.7 ± 0.4 vs 1.0 ± 1.0, NS), AST (day 1, 151 ± 372 vs 77 ± 102 U/ml, NS; exit, 80 ± 64 vs 65 ± 41 U/ml, NS), and alkaline phosphatase (day 1, 54 ± 25 vs 49 ± 15 U/ml, NS; exit, 115 ± 117 vs 151 ± 69 U/ml, NS).

Body cell mass decreased slightly in each group (oxandrolone, 33.7 ± 4.6 to 31.8 ± 4.8 kg; placebo, 32.6 ± 4.0 to 29.1 ± 3.5 kg); however, no significant differences were observed between or within groups (Figure 1). Total body water decreased significantly ($p<0.05$) in each group over the study period (oxandrolone, 58.9 ± 12.5 to 53.3 ± 14.3 L; placebo, 57.8 ± 9.6 to 47.8 ± 17.0 L). No significant differences between groups were noted in total body water at study entry or exit (Figure 2). Complete measurements could be performed in only 15 of 60 patients secondary to early hospital discharge or inability to measure due to metal placed on the patient (halos, traction).

No significant difference were seen between groups for length of hospital stay, length of ICU stay, and frequency of pneumonia, sepsis, ARDS, or MODS (Table 4).

Table 4. Clinical Outcomes

	Oxandrolone	Placebo
Mean ± SD length of hospital stay (days)	30.8 ± 17.9	27.0 ± 25.7
Mean ± SD length of ICU stay (days)	17.1 ± 7.8	15.5 ± 9.7
Mean ± SD length of mechanical ventilation (days)	11.7 ± 8.9	12.6 ± 10.0
Pneumonia (no. of patients, days)	27, 170	21, 129
Sepsis (no. of patients, days)	21, 181	22, 180
Severe sepsis (no. of patients, days)	4, 13	2, 14
SIRS (days)	283	243
ARDS (no. of patients)	3	3
MODS (no. of patients)	2	1
Death (no. of patients)	3	3

SIRS = systemic inflammatory response syndome; ARDS = acute respiratory distress syndrome; MODS = multiple organ dysfunction syndrome

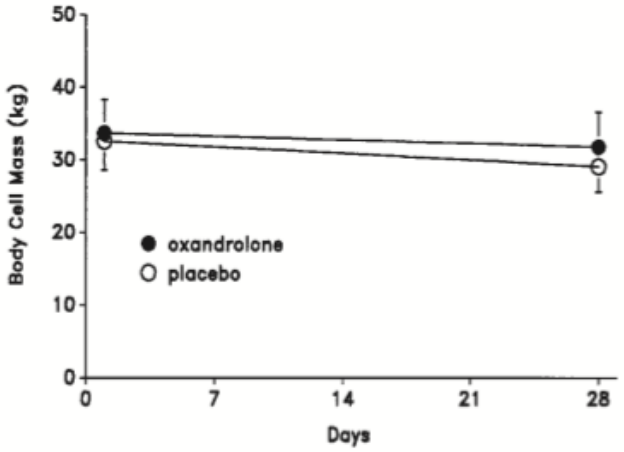

Figure 1. Body cell mass in the 15 patients (8 oxandrolone, 7 placebo) who could have bioelectrical impedance analysis done at study entry and at day 28. There was no significant difference between or within groups over time.

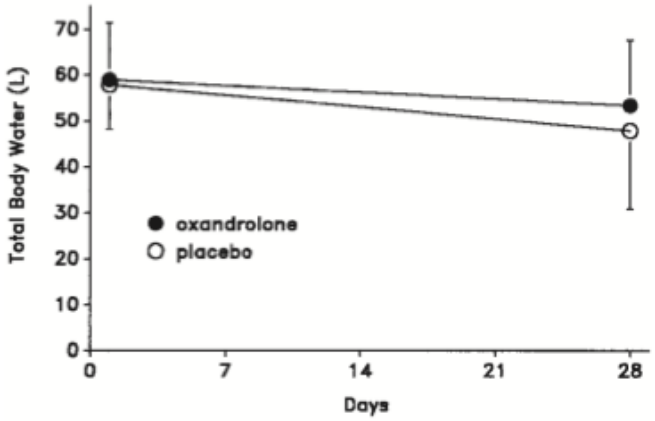

Figure 2. Total body water measurements in the 15 patients who could have bioelectrical impedance analysis done at study entry and at day 28. Total body water decreased significantly ($p<0.05$) in each group over time, but there was no significant difference between groups.

Discussion

Oxandrolone is approved for treatment of weight loss from catabolic illness including trauma injury. Our investigation of the approved dosage of oxandrolone in trauma patients who were given an enteral immune-enhancing diet showed no significant differences in nutritional or clinical outcomes compared with patients receiving placebo. Unlike this study, previous studies in critically ill patients did not measure clinical outcome; however, our study was not specifically powered to show a difference in clinical outcome. Also, our metabolic and nutritional findings are in contrast to some reports[4,5,17] and in agreement with others.[18]

A prospective, randomized, double-blind study reported decreased urinary excretion of nitrogen and 3-methylhistidine in men receiving nandrolone 50 mg on day 3 and 25 mg on day 6 after trauma compared with similar patients receiving placebo.[4] These results were supported by a prospective, randomized study in patients who received nandrolone 50 mg 3 days after sustaining moderate to severe head injury.[17] Nitrogen balance improved in patients who received intramuscular stanozolol 50 mg 24 hours before colorectal surgery in a prospective, randomized, controlled trial.[5] Nonseptic patients had significant improvements in body weight, lean body mass, and body cell mass when given intramuscular nandrolone 50 mg/week.[18] It is interesting that septic patients in that prospective, randomized, unblinded study did not have significant improvement in nutritional markers. Our patients were acutely ill from multiple trauma when they entered the study. Virtually all had SIRS and many had sepsis during the initial weeks of the study. Failure of the active drug to affect nutritional measurements early in the hospital course is consistent with findings in those septic patients.[18]

All patients in the cited studies received parenteral nutrition initially. In our study, each group received enteral nutrition initially and parenteral nutrition only when enteral intolerance was documented. Our group and others demonstrated the clinical benefits of enteral nutrition early in the clinical course after traumatic injury.[19,20] It is also notable that all patients in our study received an immune-enhancing enteral formulation that contained supplemental doses of arginine, glutamine, and α-linolenic acid. Evidence indicates that clinical outcome after trauma is improved when such formulations are administered.[21-23] Whereas the number of patients and number of days of parenteral nutrition were modestly higher in the oxandrolone group, we do not believe that this masked improvement in clinical outcome. It may have been difficult for such improvement to be observed in patients receiving oxandrolone because both groups primarily were receiving enteral nutrition with an immune-enhancing diet.

The amount of protein administered also varied between our study and others. In previous investigations, patients received approximately 70 g protein/day or 1 g/kg/day. This is similar to maintenance dosages required in health (recommended daily allowance 0.8 g/kg/day in the United States) rather than what is considered good practice in critically ill patients. Our patients had an enteral protein goal of 2.4 g/kg/day, and a substantial number of them attained this goal for several days.

Timing of anabolic steroid administration also may be an issue. Thermally injured patients given a high protein diet plus oxandrolone had increased weight gain and improved physical therapy index.[6] That study was begun when patients began recovery in an inpatient rehabilitation center. Another report from the same group described improved nitrogen retention during the acute phase of thermal injury in a small number of patients.[24] Patients with HIV-related weight loss experienced restoration of body cell mass when oxandrolone was given during a program of resistance exercise.[7] These data suggest that the agent may be most beneficial when given during the recovery phase of injury or illness. Because our study was conducted during the acute phase after traumatic injury, our patients were definitely hypercatabolic and likely hypermetabolic, although energy expenditure was not measured.

The major effect of oxandrolone during short-term administration is increased net muscle protein synthesis.[25] If this is also true for acutely ill patients, it may difficult to show improved measurements of nutrition in this population due to increased protein synthesis secondary to critical illness and administration of an enteral diet containing nutrients such as glutamine and arginine that also increase protein synthesis.

Administration of oxandrolone during the first month after multiple trauma does not result in obvious benefit in nutritional and clinical outcomes.

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