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FIVE-YEAR OUTCOMES AFTER LONG-TERM OXANDROLONE ADMINISTRATION IN SEVERELY BURNED CHILDREN: A RANDOMIZED CLINICAL TRIAL

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Abstract

Administration of oxandrolone, a non-aromatizable testosterone analog, to children for 12 months following severe burn injury has been shown to improve height, increase bone mineral content (BMC), reduce cardiac work, and augment muscle strength. Surprisingly, the increase in BMC persists well beyond the period of oxandrolone administration. This study was undertaken to determine if administration of oxandrolone for 2 years yields greater effects on long-term BMC and bone mineral density (BMD). Patients between 0 and 18 years of age with >30% of total body surface area burned were consented to an IRB-approved protocol and randomized to receive either placebo (n=84) or 0.1 mg/kg oxandrolone orally twice daily for 24 months (n=35). Patients were followed prospectively from the time of admission until 5 years post burn in a single-center, intent-to-treat setting. Height, weight, BMC, and BMD were recorded annually through 5 years post injury. The long-term administration of oxandrolone for 16±1 months postburn (range, 12.1 to 25.2 months) significantly increased whole-body (WB) BMC (p<0.02) and lumbar spine (LS) BMC (p<0.05); these effects were significantly pronounced for a longer time in patients who were in growth spurt years (7 to 18 years). When adjusted for height, gender, and age, LS BMD was

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found to significantly increase with long-term oxandrolone administration ($p<0.0009$). Fewer patients receiving oxandrolone exhibited LS BMD z scores below -2.0 as compared to controls, indicating a significantly reduced risk for future fracture with oxandrolone administration. Long-term oxandrolone patients had significantly greater height velocity than controls throughout the first 2 years postburn ($p<0.05$). No adverse side effects were attributed to the long-term administration of oxandrolone. A comparison of the current patients receiving long-term oxandrolone to previously described patients receiving 12 months of oxandrolone revealed that long-term oxandrolone administration imparted significantly greater increases in WB-BMC, WB-BMD, and LS-BMD ($p<0.05$). In conclusion, the administration of oxandrolone for up to 24 months to severely burned pediatric patients significantly improves WB BMC, LS BMC, LS BMD, and height velocity. The administration of long-term oxandrolone was more efficacious than administration for 12 months. Additionally, fewer patients in the oxandrolone cohort met the diagnostic criteria for pediatric osteoporosis, pointing to a reduced risk for future bone fracture. This study demonstrates that administering oxandrolone for up to 2 years following severe burn injury results in greater improvements in BMC, BMD, and height velocity.

Keywords

Burns; oxandrolone; hypermetabolism; outcomes; pediatric; bone mineral content; bone mineral density

Introduction

A severe burn injury induces a hypermetabolic and hypercatabolic response that is characterized by increases in cardiac work, resting energy expenditure, and muscle protein degradation (1–6). This compensatory response is accompanied by elevated hepatic glucose production and insulin resistance (4, 5, 7–10). Patients typically experience loss of lean body mass, and in children, growth is impeded. Significant reduction of bone mineral content (BMC), bone mineral density (BMD), and adipose tissue occur over time. Even several years after the injury, these children have reduced growth velocities compared to their non-burned peers (4, 11, 12). The post-burn hypermetabolic response persists for up to 2 years post-injury and can continue to negatively impact both physical and psychological well-being (4, 13, 14).

Oxandrolone, a non-aromatizable, synthetic derivative of 5- α dihydrotestosterone, has been used as an anabolic therapy during the acute care of severely burned patients (15–18). The use of oxandrolone as an anabolic agent, as opposed to testosterone, is preferred in children for several reasons. The non-aromatizable structure prevents oxandrolone from being converted to estrogen, thereby decreasing the risk of premature estrogen-dependent closure of growth plates in pediatric long bones (18, 19). Compared to testosterone, oxandrolone has limited virilizing activity and minimal hepatotoxicity (9, 20). Attenuation of the loss of lean body mass and increased BMC have been reported following administration of oxandrolone to burned patients (19).

We previously demonstrated that administering oxandrolone to severely burned pediatric patients for up to 12 months following the burn injury results in improved growth (measured

as height velocity), increased BMC, decreased cardiac work, and greater muscle strength (21, 22). Remarkably, the positive effects of oxandrolone administration on BMC endure even 4 years after oxandrolone administration has been discontinued. Here we report the results of our trial designed to determine whether the longer administration of oxandrolone, for 24 months following severe burn injury, results in greater improvements in BMC, BMD, and growth.

Methods

Subjects

This study was reviewed and approved by the Institutional Review Board at the University of Texas Medical Branch. Between 2000 and 2010, patients admitted to the Shriners Hospitals for Children®—Galveston who were 18 years of age with 30% of total body surface area (TBSA) burned were consented and randomized to a larger clinical trial (www.clinicaltrials.gov, NCT00675714) designed to assess outcomes of burn patients receiving medications aimed at attenuating the hypermetabolic response (oxandrolone, propranolol, insulin, and the combination of oxandrolone and propranolol) (Figure 1). These studies are overseen by a Data Safety and Monitoring Board comprised of representatives from the University of Texas Medical Branch and the Galveston, Texas community. The control patients were shared between the arms of these studies, causing the size of the control group to exceed that of the long-term oxandrolone group in the study reported here. Eighty four patients were randomized to the control group, and 35 patients were randomized to receive oxandrolone for 24 months (long-term oxandrolone group).

The inclusion criteria for this study required patients to be 18 years old, to have a burn covering 30% of TBSA, and to have undergone at least one surgical intervention. Patients were excluded if they sustained an anoxic brain injury; if they had a pre-existing condition such as HIV/AIDS, hepatitis, diabetes, or a 5-year history of malignancy; if the clinical determination of fertility was made; and/or if consent was not obtainable. Prior to enrollment in the study, written informed consent was obtained from the patient's parent and/or legal guardian, and assent from children 12 years of age or older.

Upon admission, patient demographics and injury characteristics were documented. Lund & Browder burn charts were used to determine the percent of TBSA burned. The diagnosis of an inhalation injury was made using bronchoscopy, which was performed on all patients 24 hours after admission (23). The length of stay and number of operating room interventions were recorded for each patient.

Oral oxandrolone administration was initiated 48 hours after the first surgical intervention at a dose 0.1 mg/kg twice daily. Patients weighing more than 50 kg received 5 mg twice daily. Drug administration compliance was reviewed at each clinical encounter. Patients randomized to receive the drug for 24 months were tracked for compliance throughout the follow-up period. Pill audits were conducted at each follow-up visit to determine patient compliance. Patients were evaluated upon admission, during acute hospitalization until discharge, at 6 month intervals throughout the first 2 years post injury, and then annually for up to 5 years. As we have already reported the results of a trial to administer oxandrolone

for 12 months post burn (21), only patients randomized to 24 months of oxandrolone who were compliant with taking their research medication for more than 12 months were included in this analysis. The patients who withdrew from the study were included in the data analysis up until their time of withdrawal.

Standard of Clinical Care

During the acute hospitalization period, patients received the standard of care for fluid resuscitation, wound excision and grafting, early ambulation, and nutritional support based on resting energy expenditure and nutritional counseling as previously described (21). At all follow-up visits, the caregivers reviewed the patient's daily dietary intake and output and medication compliance with the clinical research staff.

Anthropometric Measurements

Height and body weight measurements were recorded upon admission, at regular intervals throughout the patient's acute admission, and at all follow-up visits. All patients were weighed to the nearest 0.05 kg using a standard calibrated scale. Height was recorded to the nearest 0.1 cm using a wall stadiometer. To reduce the effect of seasonal fluctuations in longitudinal growth, we estimated annual gains in height in yearly increments from discharge to 5 years post injury. Percentiles were calculated for the individual annual gain values to assess whether the growth velocity was similar to those of unburned children. We used the maximal yearly height gain and gender-specific height velocity charts to calculate annual linear growth velocities. At each time point, the number of patients with height velocities more than 2 standard deviations below the mean was determined.

Bone Mineral Content and Bone Mineral Density

Whole-body (WB-) and lumbar spine (LS-) (L1-L4) BMD and BMC were determined using dual-energy x-ray absorptiometry (Hologic model QDR-4500W, Bedford, MA) as previously reported. To account for variations in height, age, and sex, total and LS BMD z scores were calculated using normalized values from Kalkwarf et al. (24).

Bone Age

At each follow-up visit, x-rays of the hand and knee were obtained. These were used to assess bone age and to monitor epiphyseal plate closure.

Hepatic Function

Liver size was measured for each patient upon admission, during acute hospitalization, and at follow-up visits using a HP SONOS 100 CF echocardiogram (Hewlett Packard Imaging System) with a 3.5- MHz transducer as previously described. Blood samples were collected upon admission during hospitalization, at discharge, and at all follow-up visits to assess liver enzyme abundance. Blood was drawn in serum-separator collection tubes and centrifuged for 10 minutes at 1,320 rpm. Serum was removed and stored at -80°C until analyzed (1). Nephelometry was used to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), transthyretin, and haptoglobin; insulin-like growth factor 1 (IGF-1)

was detected utilizing an enzyme-linked immunosorbent assay, as previously published (1, 2).

Statistical Analysis

The data were presented as mean $\pm$ standard error of the mean. Frequency data were reported as counts and percentages. Loess-smoothed trend was applied to all continuous data sets first for all ages (0–18 years of age) and then for patients in growth spurt years (7–18 years). Chi squared evaluations were used for categorical data. A mixed multiple regression modeled the relation of the relative age (the difference between bone age and chronological age) with gender, age at burn, TBSA, time post burn, treatment group (control versus oxandrolone), and an interaction between time post burn and treatment group, while blocking on subject to compensate for repeated measures. Time postburn was log base-2 transformed for better centering and interpretation.

All data analysis, modeling, and hypothesis testing was done in R statistical software (R Core Team, 2015, version 3.2.1), with alpha =0.05. A p value <0.05 was considered statistically significant.

The data from this trial were compared to the data from the previously published trial of the administration of oxandrolone to severely burned children for 12 months post-injury. As the data from the short-term administration of oxandrolone has already been presented elsewhere (21), only the comparison results are presented here.

Results

Study Population

This study included 119 severely burned patients randomized to control (n=84) and long-term oxandrolone (n=35). The patients' demographics and injury characteristics were not significantly different (Table 1). Oxandrolone was administered for an average of 16 ± 1 months postburn (range, 12.1 to 25.2 months). After normalizing the length of stay to the burn size, we detected no difference in the length of stay between the patient cohorts.

Bone Mineral Content and Bone Mineral Density

Significant increases in WB-BMC were found in the oxandrolone-treated patients compared to the control patients beginning at 4.5 years postburn (Figure 2a). When only patients in growth spurt years were evaluated, WB-BMC was significantly greater with oxandrolone treatment beginning 4 years postburn (Figure 2b). WB-BMD was significantly greater in oxandrolone-treated patients beginning 3 years postburn (Figure 2c). Analysis of patients in the growth spurt years revealed that increased WB-BMD occurred in only oxandrolone-treated patients beginning 2 years post-burn ($p=0.025$) (Figure 2d). In long-term oxandrolone patients, the percent increases in LS-BMC were significantly greater than those seen in the control group ($p<0.05$) (Figure 3a). When only patients in growth spurt years were evaluated, LS-BMC was significantly greater with oxandrolone treatment, beginning 2 years post burn and lasting throughout the 5 year study period (Figure 3b). At two years post-burn, the oxandrolone cohort showed a significantly higher mean z score for LS-BMD

of 0.055 (range -1.881 to 2.172) compared to controls ($p=0.0009$). The control population LS-BMD z score was -0.73 (range -2.45 to 1.66). The control cohort had a significantly higher percentage of patients (6/49, 12%) with LS-BMD z scores below -2.0, the level at which osteoporosis is diagnosed in pediatric patients (Figure 3c). By comparison, none of the patients in the oxandrolone cohort fell below -2.0 LS-BMD z score ($p=0.039$).

Anthropometric Analyses

The change in height velocities was assessed at regular intervals for both study cohorts. In both the control and oxandrolone cohorts, greater than 50% of patients were identified as having a growth deficiency at the time of discharge (Table 2). Long-term oxandrolone patients demonstrated significantly greater height velocities than controls at postburn year 1 ($p=0.0008$) and postburn year 2 ($p=0.02$).

Hepatic Function

Liver function was assessed throughout this study. Long-term oxandrolone did not significantly alter expression of ALT or AST. Transient significant increases in IGF-1, prealbumin, and haptoglobin occurred with oxandrolone as compared to the control group at 3–9 months, 6–28 months, and 6–12 months postburn, respectively (Figure 4). Liver size did not increase as a result of oxandrolone administration.

Bone Age

There was no evidence of a significant advancement in bone age versus chronological age between control and oxandrolone-treated patients. Bone age converged on chronological age by 2 to 5 years postburn.

Safety and Adverse Events

There were no adverse events in either patient cohort.

Comparison to Oxandrolone Administration for 12 Months: Bone Mineral Density and Bone Mineral Content

When the results from randomization to 24 months of oxandrolone versus 12 months of oxandrolone were compared, 24 month oxandrolone administration was found to have imparted significantly greater increases in WB-BMC, WB-BMD, and LS-BMD beginning at 3.5, 2, and 2.5 years postburn, respectively (Figure 5).

Discussion

Severe burn injury presents a unique set of challenges to clinicians owing to a rapid onset of inflammatory and hypermetabolic reactions that mobilize proteins and amino acids following the injury (9, 14, 25). Burn patients have accelerated protein turnover as evidenced by increased resting energy expenditure, elevated acute-phase proteins, and a loss of systemic protein stores (3). The burn-induced hypermetabolic response persists for upwards of 2 years in patients with burns covering >30% of TBSA (2, 26). Oxandrolone has been used to counteract the hypercatabolic response for up to 1 year following severe burn injuries (1–3, 15, 21). Our study provides evidence that longer administration of

oxandrolone imparts beneficial effects that persist for several years beyond administration of the drug.

Oxandrolone is effective in countering the growth delays associated with many childhood disorders, including Turner's syndrome (13, 27). Moreover, oxandrolone is efficacious for treating malignancy associated cachexia, neuromuscular degeneration, malnutrition, and wasting myopathy commonly associated with AIDS (28). Although each of these pathologies exhibits a unique mechanism by which protein metabolism is affected, patients with these disorders have all shown significant positive growth responses to oxandrolone. As a steroid derivative, oxandrolone induces growth through direct stereochemical binding on skeletal muscle receptors. This initiates a chain of events that result in the attenuation of protein catabolism, leading to the enhancement of lean body mass (15). The major effects seen in this long-term oxandrolone cohort, however, were on BMC, BMD, and height.

Severe burn injury is associated with a significant loss in BMC and BMD as well as a striking decrease in linear height growth velocity (1, 2, 11, 29). This was recapitulated in our current study, which showed significant decreases in BMC, BMD, and height velocity in the control group from admission to 5 years postburn. We also found that long-term administration of oxandrolone was associated with long-lasting significant improvements in WB-BMC, LS-BMC, LS-BMD, and height velocity. Porro and colleagues previously reported that, compared to the control, oxandrolone administration for 12 months significantly increased WB-BMC during growth spurt years (7–18 years) (21). Our current study confirms this finding and shows improvements in BMD as well. These improvements occur after oxandrolone administration ceases and persist until the end of this study period (5 years postburn). Patients in growth spurt years received a longer lasting benefit. In addition to having a significant effect on BMC as compared to controls, long-term oxandrolone administration increased BMC to a significantly greater degree than the previously described 12-month oxandrolone treatment. This observation was supported throughout the 5-year period reported here. Taken together, the data show that greater improvements are seen with the long-term administration of oxandrolone for up to 24 months than with shorter drug administration protocols.

Because of the adverse effect of burn injury on the metabolism of bone and calcium, researchers have used the L1–L4 vertebrae to monitor BMC. Klein and coworkers reported that there is significant BMC loss in the LS of approximately 8% over the first 24 months postinjury (30–33). The long-term oxandrolone population showed a significantly higher mean z score for spine BMD (0.055, range –1.881 to 2.172) than controls (–0.73, range –2.45 to 1.66) ($p=0.0009$). To establish whether these statistically significant spine BMD z scores were clinically relevant, we further stratified the study cohorts according to pediatric osteoporosis diagnostic criteria. The International Society for Clinical Densitometry consensus definition of pediatric osteoporosis is a BMD z score less than –2.0 with at least one identified fragility fracture (34). Thus, both study cohorts demonstrated average BMD z scores above the osteoporotic range without any evidence of fracture. However, the total number of patients in each cohort with a BMD z-score below –2.0 was significantly different. While no patients from the oxandrolone cohort fell into this group, 6 of 49 patients (12%) the control cohort had a BMD z-score below –2.0. Thus, the control population had a

significantly higher number of patients who fell into a range compatible with the diagnosis of pediatric osteoporosis and were at greater risk for future fracture than the oxandrolone group ($p=0.039$).

This study demonstrates that oxandrolone administration for up to 24 months following burn injury significantly increases WB-BMC, LS-BMC, and LS-BMD. The results of our study support the notion that increasing BMC may be the result of a direct effect of oxandrolone on bone cells (30). The lumbar spine consists of trabecular bone, whereas the whole body is comprised of 70% cortical bone. Therefore, the lumbar spine can be used to monitor the active metabolic response of trabecular bone (30–33). Our study showed that lumbar vertebrae growth remained active throughout the 2-year postburn period and can be significantly affected by oxandrolone. Because a significant increase in LS-BMD as well as WB-BMC was noted, we have postulated that oxandrolone may have a previously unknown direct effect on bone anabolism.

Over the past 50 years, oxandrolone has been used to treat growth arrest and growth retardation in patients with Down's syndrome, Trisomy 21, and Turners syndrome (13, 27, 35, 36). In our study, each patient was assessed for growth retardation by standard measurements obtained during annual encounters. The data indicated that, in both the oxandrolone and the control groups, more than 50% of patients were growth deficient at the time of discharge. Significantly higher growth velocities occurred with oxandrolone treatment at postburn years 1 and 2 as compared to controls. The substantial height growth achieved by patients administered oxandrolone for up to 24 months further supports the notion of a positive mechanism of oxandrolone working on bone cells to affect growth.

The most significant long-term effect of administering oxandrolone for up to 24 months postburn is the improvement of BMC and BMD in pediatric burn patients. When we narrowed the focus of the study to include only those patients in growth spurt years (7 to 18 years), there was a significant increase in height velocity for the group as compared to control. The finding that long-term oxandrolone has a significant effect on BMD is counter to previous studies and may perhaps indicate that longer administration periods are needed to attain these improvements. *In vitro* analyses of bone matrices have established that burn patients exhibit little osteoblastic activity from the time of injury until 14 months postburn (30–33). However, the inclusion of oxandrolone in the treatment of severely burned patients may have a direct effect on osteoblasts and other mesenchymal cells, leading to improved body composition over time (37). We did not ascertain the final height of the burned patients. Rather, we established that oxandrolone treatment increased height during the rehabilitative period. Consequently, further research efforts should be focused on determining the final height disposition of burned patients receiving long-term oxandrolone treatment.

Throughout the study period, special attention was paid to the liver size as well as acute-phase proteins and liver enzymes. Transthyretin and haptoglobin levels were significantly higher in the oxandrolone group than in the control population during the treatment period. Furthermore, IGF-1 was elevated initially and returned to normal before 1 year postburn.

Treatment did not make a difference in ALT and AST levels. Adverse events were not associated with the administration of oxandrolone in this study.

Overall, the long-term administration of oxandrolone for up to 24 months was beneficial in terms of improving BMC and BMD following a severe burn injury. However, there are challenges in achieving perfect compliance and follow-up in this population. This study was conducted in a small cohort of patients; larger studies enrolling more patients in addition to a multicenter study are needed to change the standard of care. Additionally, these studies should include burn patients of all ages. Based on our studies, efficacy may be seen only in patients who are in active growth periods or who are engaged in supervised exercise programs (including both aerobic and resistance components). The average time of administration of oxandrolone was less than 24 months; as oxandrolone is a DEA-controlled substance, we could not discharge the patients with a full 2-year allotment of the drug, which would have enabled patients to continue taking the drug even when they were unable to return to the hospital for their follow-up appointments on time. As a result, patients were unable to remain compliant and take the full 24 months of oxandrolone despite having returned to our site and participated in the study throughout the 2-year study period, and beyond. A lapse in therapy meant the patient did not get a full 24 months of oxandrolone administration, decreasing compliance with the protocol. This study allowed identification of challenges that may make compliance during the conduct of a long-term study difficult. Nevertheless, by ensuring that return visits were scheduled early enough to allow adequate time for administrative issues and having members of the research team follow-up with participants on a frequent basis, these challenges can be overcome. We believe that these limitations do not diminish the findings presented here.

Conclusion

The findings of this study provide evidence to support the administration of oxandrolone for 24 months to improve growth in severely burned pediatric patients. Chief amongst the benefits of long-term oxandrolone administration are significant increases in LS-BMC, LS-BMD, and WB-BMC, which became apparent after cessation of oxandrolone administration at or beyond the 2-year post-injury time point. Additionally, the long-term administration of oxandrolone is associated with increased height velocity for 2 years following burn injury and significant decreases in the risk of falling into the pediatric osteoporotic BMD z-score range. Based on the data presented here, we anticipate that the administration of the drug for a full 24 months can only lead to greater improvements in the endpoints included here. In conclusion, given the improvements in BMC and BMD, the administration of oxandrolone for 24 months should be tested in a larger patient population to determine whether these results apply to patients of all ages.

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Figure 1.
CONSORT diagram.

Figure 2.

The effect of oxandrolone administration on whole-body bone mineral content (WB-BMC) in (A) all patients and (B) patients 7 to 18 years of age. The effect of oxandrolone administration on whole body bone mineral density (WB-BMD) in (C) all patients and (D) patients 7 to 18 years of age. Data are represented as the loess-smoothed trend in WB-BMC and in WB-BMD, with shading indicating standard error. Hatch marks across the bottom represent the density of the sampled data at each time point. Time points at which differences are significant are indicated with wider lines ($p < 0.05$).

Figure 3.

The effect of oxandrolone administration on lumbar spine bone mineral content (LS-BMC) in (A) all patients and (B) patients 7 to 18 years of age. Data are represented as the loess-smoothed trend in LS-BMC, with shading indicating standard error. Hatch marks across the bottom represent the density of the sampled data at each time point. Time points at which differences are significant are indicated with wider lines ($p < 0.05$). (C) The percentage of patients with LS-BMD z scores below -2.0 , the level at which osteoporosis is diagnosed in pediatric patients.

Figure 4. Effect of oxandrolone on serum levels of (A) ALT, (B) AST, (C) IGF-1, (D) prealbumin, and (E) haptoglobin. Data are represented as the loess-smoothed trend, with shading indicating standard error. Hatch marks across the bottom represent the density of the sampled data at each time point. Time points at which differences are significant are indicated with wider lines ($p < 0.05$).

Figure 5.

The effect of oxandrolone administration for 24 versus 12 months on (A) whole-body bone mineral content, (B) whole-body bone mineral density, and (C) lumbar spine bone mineral density. Data are represented as the loess-smoothed trend in WB-BMC and in WB-BMD, with shading indicating standard error. Hatch marks across the bottom represent the density of the sampled data at each time point. Time points at which differences are significant are indicated with wider lines ($p < 0.05$).

Table 1

Patient demographics

Variable	Control (n=84)	Long-Term Oxandrolone (n=35)	p value
Age, yr*	7.17±0.56	8.58±0.96	0.21
Sex, male, n (%)	55 (62%)	27 (77%)	0.88
Hispanic, n (%)	77 (95%)	32 (91%)	0.60
% TBSA burned*	56±1.35	50.57±2.68	0.57
Inhalation injury, n (%)	39 (48%)	7 (20%)	0.90
Length of stay per % burn*(BAUX score)	0.45±0.031	0.44±0.027	0.74
Operations-long term, n	5.8±4.5	1.57±0.39	0.17
Exercise program, n (%)	18 (22%)	6 (17%)	0.54
Mortality, n (%)	3 (3.7%)	0 (0%)	0.81

Data are expressed as mean ±SEM. TBSA, total body surface area

Table 2

Growth distribution

Group	Postburn Year				
	Discharge				
	1	2	3	4	5
>2 SDs below mean height velocity					
Control					
		50%	24%	27%	26%
	72%	18/36	8/34	3/11	5/19
	(26/36)				
Long-Term Oxandrolone					
		5%	0%	0%	18%
	58%	1/20*	0/12	2/11	2/12
	(11/19)				
Odds Ratio					
	OR = 0.54	OR = 0.062	OR = 0	OR = 0.52	OR = 0.88
	(0.16, 1.77)	(0.002, 0.35)	(0, 0.88)	(0, 2.72)	(0.07, 6.64)

Data are presented as the number of subjects >2SDs below the mean divided by the total number of subjects measured at the time interval.

* p < 0.05 vs. control.