Five-Year Outcomes after Oxandrolone Administration in Severely Burned Children: A Randomized Clinical Trial of Safety and Efficacy

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BACKGROUND: Oxandrolone, an anabolic agent, has been administered for 1 year post burn with beneficial effects in pediatric patients. However, the long-lasting effects of this treatment have not been studied. This single-center prospective trial determined the long-term effects of 1 year of oxandrolone administration in severely burned children; assessments were continued for up to 4 years post therapy.

STUDY DESIGN: Patients 0 to 18 years old with burns covering >30% of the total body surface area were randomized to receive placebo (n = 152) or oxandrolone, 0.1 mg/kg twice daily for 12 months (n = 70). At hospital discharge, patients were randomized to a 12-week exercise program or to standard of care. Resting energy expenditure, standing height, weight, lean body mass, muscle strength, bone mineral content (BMC), cardiac work, rate pressure product, sexual maturation, and concentrations of serum inflammatory cytokines, hormones, and liver enzymes were monitored.

RESULTS: Oxandrolone substantially decreased resting energy expenditure and rate pressure product, increased insulin-like growth factor-1 secretion during the first year after burn injury, and, in combination with exercise, increased lean body mass and muscle strength considerably. Oxandrolone-treated children exhibited improved height percentile and BMC content compared with controls. The maximal effect of oxandrolone was found in children aged 7 to 18 years. No deleterious side effects were attributed to long-term administration.

CONCLUSIONS: Administration of oxandrolone improves long-term recovery of severely burned children in height, BMC, cardiac work, and muscle strength; the increase in BMC is likely to occur by means of insulin-like growth factor-1. These benefits persist for up to 5 years post burn. (J Am Coll Surg 2012;214:489–504. © 2012 by the American College of Surgeons)

Burn injury induces a hypermetabolic response that is characterized by elevations in cardiac work, metabolic rate, and muscle catabolism. Increased protein breakdown coupled with inadequate protein synthesis leads to muscle weakness and a loss of lean body mass.[1] Post-burn catabolic effects are not limited to muscle, as bone mineral content (BMC) and fat mass are decreased as well. This hypermetabolic response persists for up to 2 years after burn injury, greatly reducing quality of life for severely burned patients.[2]

Oxandrolone, a synthetic oral nonaromatizable testosterone derivative, has only 5% of the virilizing activity and low hepatotoxicity when compared with testosterone. After

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Abbreviations and Acronyms

BMC = bone mineral content
BMD = bone mineral density
CO = cardiac output
HR = heart rate
IGF-1 = insulin-like growth factor-1
IGFBP = insulin-like growth factor-binding protein
IL = interleukin
REE = resting energy expenditure
RPP = rate pressure product
TBSA = total body surface area

administration, oxandrolone reaches peak serum concentrations within 1 hour and is excreted through the urine. Oxandrolone binds to androgen receptors in the skeletal muscle to initiate protein synthesis and anabolism. Because oxandrolone cannot be aromatized to estrogen, the likelihood of estrogen-dependent bone-age advancement is reduced, making oxandrolone a safe therapeutic approach for growing children.[3-5]

In children with Turner syndrome and other growth-related conditions, oxandrolone has been used successfully for many decades to safely treat growth delays.[6-10] More recently, oxandrolone has been used to induce anabolism in patients experiencing muscle wasting associated with AIDS, major surgery, infections, malnutrition, neuromuscular disorders, or thermal injury.[11,12] Oxandrolone is the only androgenic steroid approved by the US Food and Drug Administration to maintain body weight in these catabolic states.[3] These studies have demonstrated that oxandrolone has an excellent safety profile and is well tolerated by patients.

We have previously shown in severely burned children that short-term administration of oxandrolone during the acute phase of burn injury increases net muscle protein balance, maintains lean body mass, and shortens ICU stay.[1,13-15] Additionally, short-term oxandrolone use is associated with elevation of liver enzymes aspartate aminotransferase and alanine aminotransferase from 17 to 40 days post burn.[13] Amino acid use is improved for up to 6 months post burn in patients randomized to oxandrolone treatment.[16] In a small group of severely burned children, administration of oxandrolone for 1 year post burn increased lean body mass, BMC, muscle strength, heights, and weights. These benefits lasted for at least a full year after discontinuation of oxandrolone.[17,18] The addition of a 12-week exercise program to 1 year of oxandrolone therapy provided an even greater increase in weight and lean body mass.[19]

We conducted a single-center prospective randomized controlled trial in massively burned pediatric patients to investigate the effects of oxandrolone administration for 1 year post burn on growth, body composition, muscle strength, resting energy expenditure (REE), liver and cardiac function, serum markers, hormones, bone mass, and sexual maturation. We present the data from this trial, including data gathered up to 5 years post burn, that relate to the safety and efficacy of the drug. A subset of these patients also underwent a 12-week exercise program to determine if exercise, in combination with oxandrolone, affects lean body mass and BMC. These data are presented as well.

METHODS

Patients

Two thousand eight hundred and twenty-one severely burned children were admitted to our institution from 2000 to 2010. Of these, 516 patients with burns >30% of the total body surface area (TBSA) were consented and randomized to studies of various anabolic agents administered acutely and long-term post injury. Seventy patients were randomized to receive oxandrolone, 152 to the control group, and 294 to other ongoing studies (Fig. 1). Control patients outnumbered oxandrolone-treated patients due to the balanced design of the randomization schedule, to share control subjects with all studies in a time contiguous fashion.

Patients 0 to 18 years of age at the time of the burn, with >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 HIV, AIDS, 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 and given orally at a dosage of 0.1 mg/kg twice a day for 1 full year (BTG Pharmaceuticals). Four patients over 50 kg received 5 mg twice daily. Patients were assessed at admission; during acute hospitalization; at discharge; at 6, 9, 12, 18, and 24 months after burn; and annually thereafter. Patients who withdrew from the study were included in the data analysis up to the time of withdrawal. This study was part of a large clinical trial (www.clinicaltrials.gov, NCT00675714) evaluating the outcomes of burn survivors after administration of therapeutic agents such as oxandrolone, propranolol, insulin, and the combination of oxandrolone and propranolol. Informed written consent 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. This study adhered to