EFFECTS OF OXANDROLONE ON LEAN BODY MASS (LBM) IN SEVERE BURN PATIENTS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

EFFETS DE L'OXANDROLONE SUR LA MASSE MAIGRE (MM) DU BRÛLÉ GRAVE : UNE ÉTUDE RANDOMISÉE EN DOUBLE AVEUGLE CONTRE PLACEBO

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SUMMARY. In severe burns, hyper-metabolic conditions due to elevation of pro-inflammatory cytokines and stress hormones usually occur. Unregulated hypermetabolism can lead to muscle protein catabolism, inducing weakness, infection, and delayed wound healing. Oxandrolone is known as an anabolic agent with minor side effects. This study aims to determine the effect of oxandrolone on lean body mass (LBM) in severe burn patients. A randomized, double blind and placebo controlled trial was conducted in the burn centre of the Dr. Soetomo Hospital. Severe burn patients who met the inclusion criteria were randomized into two groups, oxandrolone and placebo group. Oxandrolone was given with a dose 0.1 mg/kg twice a day for 14 consecutive days. Estimated lean body mass (eLBM) for each group was measured on admission (day 0) and day 14. Fourteen burn patients were enrolled in this study. Lean body mass reduced significantly from 48.69±7.71 to 46.70±7.96 in the placebo group (p-value 0.008) by independent t-test. There was no significant decrease of LBM in the oxandrolone group. Delta LBM (Δ eLBM) before and after treatment was 0.38±1.64 in the oxandrolone group, and -1.32±1.23 in the placebo group (p-value = 0.049). There were no adverse effects during the administration to the oxandrolone group. In severe burn patients, oxandrolone could prevent reduction of LBM compared to placebo and is relatively safe. These findings suggest the efficacy of oxandrolone in preventing muscle catabolism as a part of hypermetabolism in burn patients.

Keywords: oxandrolone, hypermetabolism, severe burn injury, lean body mass

RÉSUMÉ. *Un état hypermétabolique, dû à l'élévation des cytokines pro- inflammatoires et des hormones du stress, est habituel. Il peut être à l'origine d'un catabolisme musculaire (responsable d'une faiblesse musculaire), d'infections et de retard de cicatrisation. L'oxandrolone est un agent anabolisant ayant peu d'effets secondaires. Cette étude a pour but d'étudier son effet sur la MM des brûlés graves. Il s'agit d'une étude randomisée en double aveugle contre placebo, conduite dans le CTB de l'hôpital Dr Soetomo auprès de 14 patients. L'oxandrolone était prescrite à la posologie de 0,1 mg/kg x 2/j pendant 14 j. La MM estimée (MMe) était notée à l'admission (J0) et à la fin du traitement (J14). La MMe baissait significativement de 48,69 +/- 7,71 à 46,70 +/- 7,96 kg (p = 0,008 ; test t) chez les témoins quand cette variation n'était pas significative sous oxandrolone. La variation de MM (ΔMM) entre J0 et J14 était de 0,38 +/- 1,64 kg dans le groupe oxandrolone et de – 1,32 +/- 1,23 kg dans le groupe témoin (p = 0,049). Aucun effet indésirable n'a été observé dans le groupe oxandrolone. Chez les patients gravement brûlés, l'oxandrolone pourrait prévenir la perte de MM et est relativement sûre, nos données suggérant son efficacité sur la lyse musculaire liée à leur hypermétabolisme.*

Mots-clés : *oxandrolone, brûlure sévère, hypermétabolisme, masse maigre*

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Introduction

Burns are tissue damage resulting in the loss of some or all layers of the skin barrier. Severe burn alters physiologic derangements affected by a state of rapidly increasing hypermetabolism, including reduced lean body mass, insulin resistance, delayed wound healing and increased systemic infection. Unregulated hypermetabolism could lead to multiorgan failure and eventually death.[1] Early excision or debridement of burned tissue to remove dead tissue or debris and to inhibit the inflammatory process has decreased the risk of infection and length of stay.[2] However, severe burn patients who survive exhibit a hypermetabolic response for a long time, even after discharge from hospital for up to eight months after injury, and characterized by muscle wasting, decreased bone mineral density and retarded growth, especially in children.[3]

Muscle wasting is a condition of losing muscle mass due to muscle component breakdown, especially protein. Muscle wasting can lead to a reduction in lean body mass (LBM), so that a significant decrease in LBM can increase the risk of death in burn patients. A severe burn will cause a large increase in the catabolic rate, leading to lean mass consumption and a decrease in protein reserves. Decreased muscle mass and lean body mass will lead to deficiencies in wound healing and musculoskeletal function.[4-6] Testosterone analogs have been reported to be used as substances that can reduce protein loss and stimulate anabolism, one of which is oxandrolone as an anabolic agent.[7]

Oxandrolone is a synthetic testosterone analog with a low androgenic effect and fewer hepatotoxicity properties. Previous study has shown that oxandrolone is successfully used for children with Turner syndrome, cachexia, alcoholic hepatitis, AIDS and other growth disturbance diseases.[8] Oxandrolone is currently used in several patient populations, including burns, to restore weight loss caused by injury or illness. The rate of lean mass gain in the post-burn recovery period using oxandrolone and nutrition has been reported to be four times higher than that of nutrition alone, with no significant complications.[9]

Some instruments such as magnetic resonance and dual absorptiometry x-ray (DXA) and computed tomography (CT) are used to calculate LBM. However, these methods are expensive and there is limited access in clinical practice. Therefore, a cheap and straightforward approach was required to assess LBM. The anthropometric-based equation to predict LBM can be used as an alternative method. A study by Yu et al. reported that the anthropometric prediction equation offers an alternative to assess LBM in healthy adults when access to CT or DXA is limited.[10]

So far in Indonesia, no study has evaluated the efficacy of oxandrolone in burn patients. Based on this background, the aim of this study is to investigate the efficacy of oxandrolone on lean body mass in severe burn patients using anthropometric estimation in the Indonesian population.

Materials and methods

This fourteen-day randomized, double-blind, placebo-controlled, and mono center study was conducted at the burn unit of Dr. Soetomo Hospital, East Java, Indonesia. This study was performed under the Ethical Committee of Dr. Soetomo Hospital with the registration number: 157/KEPK/IX/2019. Severe adult burn patients admitted to the burn unit of the Dr. Soetomo Hospital between June 2019 and September 2020 were included in the study. Before study enrollment, the patient's family or guardian was informed about the purpose of the study and the risks and benefits, and asked to fill in the written informed consent.

The inclusion criteria in this study were as follows: burn patients aged more than 18 years old; TBSA ≥25% and less than 72 hours after burning; patients were not to be under medications that might interfere with the result, such as testosterone, recombinant growth hormone, beta-blocker or diabetes medication; patients were able to feed orally or enterally. The exclusion criteria were burned patients with electrical injury, pregnancy or breastfeeding, and patients with prostate and breast carcinoma history. Patients would be dropped out if they were discharged from the hospital or expired before completing the 14 days of the study.

The subjects were assigned by simple random allocation into two groups and followed for 14 con-

secutive days. Oxandrolone with a dose of 0.1 mg/kg was given twice daily in group 1 and initiated after resuscitation, whereas subjects in group 2 received a placebo. The pharmacy department's allocation was conducted in the burn unit and kept secret until the study was completely finished. None of the researchers in this study were included in the distribution of subjects. Both oxandrolone and placebo were packaged in identical capsules and differentiated by a code ("1" or "2"). The researcher and the subjects were blinded to the two identical capsules' content during the study period. A third party who was related to the study conducted the blinding codes.

All of the patients received ringer lactate solution using modified Parkland formula within 24 hours of the initial injury. Enteral nutrition was slowly introduced within 24 hours of injury, and full nutrition was set within two days. Enteral and parenteral nutrition were given in this study providing a carbohydrate composition of 55-60% of total daily calories, protein 1.5-2 g/kg/day or 20-25% of total calories, and fat less than 25% of total calories. Each sachet of enteral nutrition contains 200 kkcal of calories (PANTERAL®). Calorie needs in burn patients for the acute phase are 20-25 kcal/kg/day, while for the maintenance phase, 25-30 kcal/kg/day. The patients underwent debridement every five to seven days more than once. Vital signs, urine output and complete blood count were regularly observed during hospitalization until discharge.

This study's primary outcome was estimated lean body mass (LBM) before and after each treatment, and the secondary outcome was the incidence of side effects after administration of oxandrolone. To calculate LBM, an estimated equation of LBM based on the formula for Asians[11] was used, as follows:

LBM male = -25.498 – 0.051 (age) + 0.312 (height) + 0.263 (weight) + 0.373 (body mass index)

LBM female = 18.866 + 0.634 (weight) – 0.771 (body mass index)

The anthropometric parameters, including body weight, height and body mass index were recorded twice, on admission and after two weeks of treatment. Body mass index (BMI) was calculated by dividing body weight in kilogram with height in m^2.

This study's sample size was calculated based on the published level of lean body mass in burn patients. To assess the normality of the variables, the Kolmogorov-Smirnov was used. To determine the differences in all baseline data and variables between the two groups, we used an independent t-test. To determine the different variables before and after treatment for each group, we used paired t-test. Calculated p-values were interpreted as statistically significant if they were less than 0.05.

Results

Fourteen severely burned adult patients were included in this study. Seven burn patients were enrolled for each group. Numerical variables were normally distributed by Kolmogorov-smirnov test with p-value >0.05. The demographic of the patients is shown in *Table I*. There was no significant difference in sex, age and total burn surface area (TBSA) between the two groups (p > 0.05).

Table I - Demographic data for each group

Variables	Oxandrolone (n=7)	Placebo (n=7)	p-value
Sex			
Male	4 (51.1%)	5 (71.4%)	0.577
Female	3 (42.9%)	2 (28.6%)	
Age (years)	40,86 ± 13,16	42,43 ± 14,59	0,836
TBSA (%)	35,71 ± 13,59	33,79 ± 12,07	0,812

The anthropometric parameters including body weight, height and estimated LBM as well as the differences before and after treatment in the oxandrolone group and placebo group are shown in *Table II* and *Table III*, respectively.

Table II - Estimated LBM in the oxandrolone group at day 0 and day 14

Variables	H-0	H-14	p-value
Weight (kg)	59,71 ± 6,05	59,14 ± 6,74	0,535
BMI (kg/m^2)	21,93 ± 2,23	21,74 ± 2,36	0,594
e LBM	44,60 ± 5,22	45,16 ± 6,00	0,564

Table III - Estimated LBM in the placebo group at day 0 and day 14

Variables	H-0	H-14	p-value
Weight (kg)	68,71 ± 9,59	63,00 ± 11,4	0,006
BMI (kg/m^2)	25,24 ± 2,64	23,22 ± 3,47	0,006
e LBM	48,69 ± 7,71	46,70 ± 7,96	0,008

In baseline of e LBM at day 0, there was no difference between the two groups by independent t-test (p-value=0.352). The delta (Δ eLBM) of each group before and after treatment is shown in *Fig. 1*. There was a significant difference in Δ eLBM by independent t-test (p-value= 0.049). The oxandrolone group has a positive mean of Δ eLBM. There were no side effects of oxandrolone administration during this study.

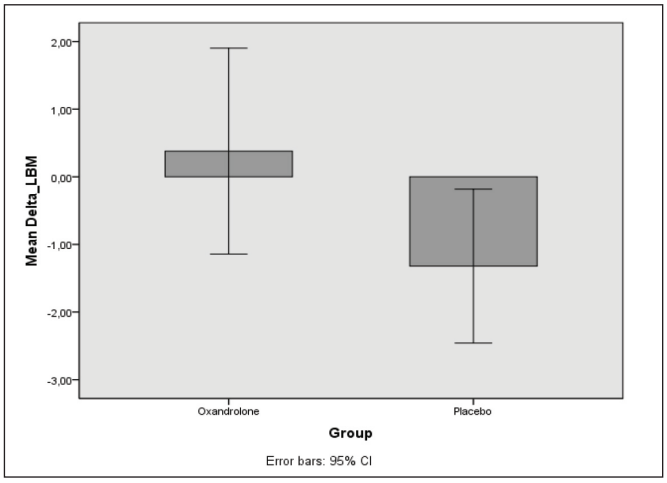

Fig. 1 - Mean delta of LBM between the two groups

Discussion

This randomized placebo-controlled trial is the first study in Indonesia among adult burn patients evaluating the efficacy of oxandrolone on lean body mass. This study included fourteen severely burned patients with average TBSA more than 30%. Severe burn patients with TBSA >20% are characterized by an increased insulin resistance, myocardial oxygen consumption, risk of infection, catabolic rates, and decreased protein synthesis. The most common catabolic rates were shown in reduced body weight, especially lean body mass.[12] Several studies reported that the administration of anabolic steroid, oxandrolone, has positive impacts in burn patients to prevent muscle wasting. Williams et al. reported that loss to lean body mass will lead to immune dysfunction of 10%, delayed wound healing of 20%, systemic infection of 30%, and death of 40% of burn patients.[6]

Oxandrolone was approved by the FDA for the therapy of trauma, severe illness, and disorders of muscle wasting. Oxandrolone has been used to increase body weight in HIV/AIDS patient-associated myopathy with muscle wasting, and gain of LBM in patients with chronic obstructive pulmonary disease in a cachexic condition. Furthermore, oxandrolone was used to improve growth in children with cystic fibrosis.[13] A study by Berger et al. reported that the administration of oxandrolone at a dose both 5 mg/day and 15mg/day had a beneficial impact on maintaining and gaining body weight in HIV patients suffering from weakness and wasting.[14] Because of its ability to counteract the catabolic condition, oxandrolone has been used as an anabolic steroid in severely burned patients in recent decades.[15] Among anabolic androgens, oxandrolone was given orally with minimal androgenic activity. Oxandrolone has anabolic activity by binding to its androgen receptor in skeletal muscle and inducing muscle protein synthesis. Oxandrolone also inhibits muscle catabolism by working as a glucocorticoid receptor antagonist.[16] Oxandrolone has a high anabolic activity compared to testosterone and methytestosterone with a ratio anabolic: androgenic of 10:1.[17]

According to our results, the treatment with oxandrolone in a dose 0.1mg/kg bid orally for 14 consecutive days improved the clinical outcomes of burn patients by preventing loss of lean body mass during hospitalization compared to placebo. Total body weight is a combination of fat mass and fat-free mass. Fat-free mass (FFM) consists of bones, muscles, vital extracellular organs and fluids. LBM is similar to FFM, but with the inclusion of lipids in the cellular membrane, though it only accounts for a fraction of the total body weight (up to 3% in men and 5% in women).[18] In some literature, bone mass is sometimes included in LBM and in some other literature it is not included.[19,20] Our study was similar to several studies that indicated that the use of oxandrolone vs. a control (placebo or not) has significant advantages, such as less body mass loss, nitrogen loss, and donor tissue healing time.[21-25] However, there were some differences to our data in time to administer oxandrolone in some studies. In a study by Demling in 1999,[22] oxandrolone was given at day 7 to 10 after burns, and in Demling et al. in 2000,[23]

oxandrolone was given at day 2 to 4 after burns. Meanwhile, in our study oxandrolone was given shortly on admission to hospital. In our study, we used the estimated LBM with the equation for Asians. Contemporary south Asians generally have a lower lean mass (organ and lean muscle) relative to the physique and total body mass of Europeans, which may partially explain why they develop non communicable disease at a lower BMI than in other populations.[26]

A meta-analysis study reported that when oxandrolone was used in burn patients, there were significant benefits in terms of less loss of corporal mass, nitrogen loss, and donor area healing time when compared to a control group or placebo.[9] According to Demling et al., oxandrolone is an excellent alternative for burn metabolic treatment. Oxandrolone has improved outcome measures beyond what was possible in control patients already receiving optimal clinical burn therapy. Furthermore, oxandrolone therapy is not only safe but also cheap, costing only 10% of an equivalent anabolic dose of recombinant human growth hormone.[21-23]

Amino acid precursors for improved muscle protein synthesis may come from blood or muscle protein breakdown. The efficacy of incorporating amino acid precursors from both sources into protein is referred to as the performance of muscle protein synthesis. Oxandrolone did not affect inward transport in the current study, but caused an increase in protease levels. The use of free intracellular amino acids produced by protein breakdown was improved by oxandrolone. Consequently, protein synthesis was enhanced whereas protein breakdown remained stable, leading to a net balance of muscle protein metabolism.

Even though in our study we did not analyze the effects of oxandrolone in burn patients with inhalation trauma, a study by Sousse et al. reported that oxandrolone in a dose 0.1 mg/kg/day bid for 12 months improved lung function in children with burns. The maximum voluntary ventilation of oxandrolone-treated subjects was significantly higher (98±53L/min vs. 115±56 without treatment, p-value =0.03). The maximum expired ventilation (VEmax) was significantly higher in oxandrolone-treated subjects than in untreated subjects during maximal exercise (32.0±8.7 L/min vs. 43.7±13.6 with treatment, p-value =0.02).[27] It was suggested that the duration of hospital stay of severe burn patients is longer than that of those with moderate burns. The study by Wolf et al. reported that the duration of stay in the oxandrolone 10mg bid group was significantly shorter (31.6±3.1 days) compared to placebo (43.3±5.3 days). Operating procedures in the oxandrolone group decreased significantly and indicated that oxandrolone accelerated wound healing.[25]

In our study, we found no adverse effects in the oxandrolone group. Oxandrolone is less metabolized in the liver compared to other anabolic agents, and therefore the incidence of hepatotoxicity may be lower. This is because oxandrolone has the lactone group in its chemical structure, making it more resistant in liver biotransformation. Approximately 28% of oxandrolone dose is excreted as a parent drug or unchanged and unconjugated in the urine. Several studies reported the administration of oxandrolone in burn patients with a dose 10-20 mg bid, and showed that adverse effects in hepatic dysfunction was transient or mild compared to placebo. A study by Hart et al. reported that after the administration of oxandrolone in severe burn children in a dose 0.1 mg/kg for 5 days, there were no differences of adverse effects in liver function test before and after treatment in the oxandrolone and the control group.[28] A recent meta-analysis stated that oxandrolone was not associated with mortality or impaired liver function. Oxandrolone reduced length of stay of burn patients in hospital.[29,30] Hepatic dysfunction was observed after long treatment and a high dose of oxandrolone for several diseases. Fortunately, oxandrolone was used in burn settings for a short time period.

Little has been identified about the risk factors that could lead to the development of transaminitis or hepatic dysfunction stimulated by oxandrolone. The McCullough study is the only study published in the literature to characterize possible risk factors associated with hepatic dysfunction in patients receiving oxandrolone therapy. In addition, there was no difference in the incidence of hepatic dysfunction when comparing TBSA percent burn. The small study of only 14 patients in the oxandrolone group, the different oxandrolone dosage therapies of 5 mg

and 10 mg twice daily, and the overall lower burn severity (mean of TBSA 15–19%) is a limiting factor when determining potential risk factors.[31]

There are several limitations to this study. The first is the limited number of samples so that the results obtained cannot describe the overall patient population of burns. Second, we did not report the patients' daily calorie intake and transaminase to assess the hepatotoxicity of oxandrolone. However, a study conducted by Hart et al. reported no differences in calorie intake, protein intake, and albumin during the study period in burn patients who received oxandrolone or placebo. Each burn patient in that study received enteral nutrition with Vivonex TEN containing 82% carbohydrate, 15% protein, and 3% fat. Caloric intake/day was administered at a rate calculated to deliver 1,500 kcal/m2 TBSA burned. Resting energy expenditure as a percentage of basal metabolic rate was 150±15% in the placebo group and 141±14% in the oxandrolone group. The enteral nutrition effectively achieved a high-calorie and high-protein intake and significantly improved nutritional status, as evidenced by an increase in dietary indices.[28]

Conclusion

This study showed that the administration of oxandrolone in severely burned patients could prevent loss of lean body mass as a promising choice to regulate hypermetabolism and is relatively safe. Estimated equation of LBM using anthropometric measurement is a low cost and practical method to assess LBM. Caution should be taken regards hepatic dysfunction by closely monitoring transaminase. Further research is needed to clarify the efficacy and safety of oxandrolone in clinical outcomes among Indonesian burn patients.

BIBLIOGRAPHY

1 Jeschke MG, Tilley R, Centre B: Post-burn hypermetabolism: past, present and future. J Burn Care Res, 37(2): 86-96, 2017.
2 P Gacto-Sanchez: Surgical treatment and management of the severely burn patient: review and update. J Wound Care, 41(6): 356-64, 2017.
3 Gauglitz GG, Finnerty CC, Herndon DN: Modulation of the hypermetabolic response after burn injury. In: Herndon DN (ed.): "Total Burn Care", pp. 355-360, Elsevier Saunders, London, 2012.
4 Jeschke MD, Chinkes DL, Finnerty CC: Pathophysiologic response to severe burn injury. Ann Surg, 208(4): 489-502, 2008.
5 Pereira C, Murphy K, Jeschke MG: Post burn muscle wasting and the effects of treatment. Int J Biochem Cell Biol, 37(10): 1948-1961, 2005.
6 Willams FN, Jeschke MG, Chinkes DL: Modulation of hypermetabolic response to trauma: temperature, nutrition, and drugs. J Am Coll Surg, 208(4): 387-401, 2009.
7 Porro LJ, Herndon DN, Rodriguez NA: Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg, 214(4): 489-502, 2012.
8 Rojas Y, Finnerty CC, Radhakrishnan RS: Burns: an update on current pharmacotherapy. Expert Opinion on Pharmacotherapy, 13(17): 2485-2494, 2013.
9 Real DS, Reis RP, Piccolo MS: Oxandrolone use in adult burn patients. Systematic review and meta-analysis. Acta Ciruriga Brasileira, 29(supl.3): 68-76, 2014.
10 Yu S, Visvanathan T, Filed J: Lean body mass: the development and validation of prediction equations in healthy adults. BMC Pharmacology and Toxicology, 14: 53, 2013.
11 Li J, Shang J, Guo B: Establishment of prediction equations of lean body mass suitable for Chinese adults. Biomed Research International. doi:doi.org/10.1155/2019/175794, 2019.
12 Atiyeh BS, Gunn SWA, Dibo SA: Nutritional and pharmacological modulation of the metabolic and response of severely burned patients: review of the literature (part 1*). Ann Burns Fire Disasters, 21(2): 63-72, 2008.
13 Orr R, Singh MF: The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders. Drugs, 64(7): 725-750, 2004.
14 Berger JR, Pall L, Hall CD, Simpson DM: Oxandrolone in AIDS-wasting myopathy. AIDS, 10(14): 1657-62, 1996.
15 Miller JT, Btaiche IF: Oxandrolone treatment in adults with severe thermal injury. Pharmacotherapy, 29(2): 213-226, 2009.
16 Thum T, Springer J: Breakthrough in cachexia treatment through a novel selective androgen receptor modulator?! J Cachexia Sarcopenia Muscle, 2(3): 121-123, 2011.
17 Kuhn CM: Anabolic steroids. Recent Prog Horm Res, 57: 411-34, 2002.
18 Janmahasatian S, Duffull SB, Ash S, Ward LC et al.: Quantification of lean bodyweight. Clin Pharmacokinet, 44(10): 1051-1065, 2005.
19 Prado CM, Baracos VE, McCargar LJ: Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res, 15(8): 2920-2926, 2009.
20 Mourtzakis M, Prado CM, Lieffers JR: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab, 33(5): 997-1006, 2008.

21 Demling R, DeSanti L: Oxandrolone, an anabolic steroid significantly increases the rate of weight gain in the recovery phase after major burns. J Trauma, 43: 47-52, 1997.
22 Demling R: Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. Burns, 25: 215-21, 1999.
23 Demling R, Orgill PD: The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. J Critical Care, 15(1): 12-7, 2000.
24 Demling R, DeSanti: Oxandrolone induced lean mass gain during recovery from severe burn is maintained after discontinuation of the anabolic steroid. Burns, 29: 793-7, 2003.
25 Wolf SE, Edelman LS, Kemalyan N: Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. J Burn Care Res, 27(2): 131-9, 2006.
26 Rush EC, Freitas I, Plank LD: Body size, body composition and fat distribution: comparative analysis of European, Maori, Pacific Island and Asian Indian Adults. Br J Nutr, 102: 632-641, 2009.
27 Sousse LE, Herndon DN, Mlcak RP: Long-term administration of oxandrolone improves lung function in pediatric burned patients. J Burn Care Res, 37: 273-277, 2016.
28 Hart DW, Wolf SE, Ramzy PI: Anabolic effects of oxandrolone after severe burn. Ann Surg, 233(4): 556-564, 2001.
29 Ring J, Heinelt M, Sharma S: Oxandrolone in the treatment of burn injuries: a systematic review and meta-analysis. J Burn Care Res, 41(1): 190-199, 2020.
30 Li H, Guo Y, Yang Z, Roy M: The efficacy and safety of oxandrolone treatment for patients with severe burns: a systematic review and meta-analysis. Burns, DOI: dx.doi.org/10/1016/j.burns.2015.08.023, 2015
31 McCullough MC, Namias N, Schulman C: Incidence of hepatic dysfunction is equivalent in burn patients receiving oxandolone and controls. J Burn Care Res, 28(3): 412-420, 2007.