

Oxandrolone use in adult burn patients. Systematic review and meta-analysis

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ABSTRACT

PURPOSE: This study is a systematic literature review and meta-analysis concerning the use of a testosterone synthetic analog, oxandrolone, and its use in severe adult burns.

METHODS: Randomized prospective clinical studies, in English, Portuguese or Spanish, were sought on the following databases: MEDLINE, COCHRANE, EMBASE and LILACS. There was no restriction in relation to the publication date.

RESULTS: This search produced 24 studies on MEDLINE and twelve articles were presented on the COCHRANE database. Sixteen were excluded due to the title not being related to this search or by including children. Of the eighth residual studies, after adaptation to the inclusion criteria, only four were selected. After analyzing the results, two were discarded since they did not present adequate patient characterization and the facts on these articles were analyzed differently from the others, hindering the meta-analysis.

CONCLUSION: The analysis of the available data demonstrated significant benefits ($p < 0.05$) considering lesser loss of corporal mass, lesser nitrogen loss, and shorter donor area healing time, when Oxandrolone was used, comparatively with the control group (placebo or not).

Key words: Oxandrolone; Burns; Adults; Systematic review; Meta-analysis.

Introduction

Burn injuries and their sequelae have been present for centuries as major importance world problems. It is referred that over 1.2 million individuals will sustain a burn injury every year in the USA, being that the majority of these lesions are small burns, treated in the ambulatory. However, approximately 60,000 cases are moderate or severe and require hospitalization for their treatment. Furthermore, it is estimated that 5,000 deaths occur every year in the USA due to Burns or their complications¹.

Corroborating to ratify the importance of the burn patient, and the need for improvements in their care, Bull and Fisher, in 1949, reported a 50% mortality rate for children (0-14) with 49% TBSA, for young adults (15-44) with 46% TBSA, for individuals between 45 and 64 with a 27% TBSA and for those older than 65, 10% TBSA². These statistics have improved considerably with the advances in critical patients care, with current data showing a 50% mortality rate in children up to 14 with 98% TBSA and in young adults with over 75%TBSA^{3,4}.

Data available through the Brazilian Burn Society indicate that, in Brazil, there are one million burn cases each year; 200 thousand are seen in emergency services and 40 thousand will need hospital admission. Burns area amongst the main external death causes in Brazil, second only to other violent causes, such as traffic accidents and manslaughter⁵. A study on a hospital in Brasilia demonstrated a 6.2% death rate in burn patients admitted to an emergency hospital⁶.

As shown, it is noted the importance of the optimization of burn patient care in its acute phase, in intensive care, as well as in the recovering and rehabilitation phases, not forgetting that prevention is the best treatment.

Severe Burns will cause a great increment in catabolic rates, leading to lean mass consumption and decrease in protein reserve. Decreasing the lean mass will lead to a deficiency in wound healing and in muscle-skeletal function⁷⁻¹³. Testosterone analogs have been reported in the literature as substances which will decrease protein loss and stimulate anabolism¹⁴⁻¹⁸.

Oxandrolone is a synthetic analog, 17 alpha-methyl, derived from testosterone with frequent use in a large number of critical patients, such as advanced hepatopathies, HIV, cardiac cachexia, major Burns and other hyper catabolic patients, showing restoration in lean mass together with improved nutrition¹⁷⁻²⁰.

However, few studies permeate oxandrolone anti-catabolic action on major burn patients²¹⁻²³. This action consists in diminishing protein and lean mass loss, shortening wound healing

time and donor area reepithelisation, as well as possible hospital stay decrease^{16,17}.

Based on the knowledge related to this subject, the objective of this systematic review study is to list the effects of oxandrolone in major adult burn patients, since there are few studies related to this theme on the literature, what rectifies the lack of protocol and systematization for its use in major burns units. As such, this review intends to serve as evidence for the secure and systematic use of Oxandrolone in the acute treatment as well as in the rehabilitation of adult patients with severe burns.

Objectives

The objective of this study is to respond the question about the use of oxandrolone in adult patients with severe burns, in relation to the time of wound healing of donor site, the nitrogen loss and the body mass loss.

Methods

To attain this objective, a selection of studies was performed within the main databases and its results were analyzed through a meta-analysis, according to the protocols of COCHRANE²⁵.

Selection Criteria

For selection criteria, the search was performed within the main health databases: MEDLINE, COCHRANE, EMBASE e LILACS, the period of February 2014, using the key words: severe burn and oxandrolone. As filters, language was restricted to Portuguese, English and Spanish.

The first selection was done through reading the titles, excluding all articles which had children in the study. Later, other factor was the study design, being that clinical, randomized and prospective studies were selected.

As results,

- MEDLINE: the search produced 24 articles. Nine were excluded due to the title not being related to this search and seven were excluded because they included studies in children. Of the eight residual studies, two were literature reviews which were also excluded since they did not obey the inclusion criteria and six clinical trials, one was excluded for being retrospective and observational and other was selected to the systematic review. Of these five

articles, four were included in the systematic review and one excluded after reading the abstract because it was not about the subject of this review.

- COCHRANE: 12 articles were presented: two systematic reviews were excluded for not being related to the search criteria of this research and ten controlled studies, of which five were excluded for being related to children or not corresponding to the theme. Four presented correspondence with those of MEDLINE
- The other bases surveyed did not return any results.

Study Type

The four selected studies according to the search criteria were:

- Demling R. (1999)²¹: Prospective, randomized, case controlled study
- Demling R, Orgill PD. (2000)²²: Prospective, randomized, double-blind, case controlled study
- Demling R, DeSanti L. (2003)²³: Prospective, randomized, case controlled study
- Wolf SE et al. (2006)²⁴: Prospective, multicentre, randomized, double blind, case-controlled study

Study subjects

Subject groups, per study:

- Demling R. (1999)²¹: Sequential patients who fitted the criteria for the use of anabolic agent, admitted to the burn center in 1996 and 1997. Patients were randomized either to a group using Human Growth Hormone (HGH) or Oxandrolone, The patients with major burns whom did not fit the inclusion criteria for either group were the control group.

The groups were characterized as such:

1. Deep burns, 2nd or 3rd degree over 50% TBSA, with at least half of the area needing skin grafting.
 2. Deep burns, 2nd and 3rd degree over 25% TBSA, with comorbidities, such as: older than 60, malnutrition and adults with diabetes.
- Demling R, Orgill PD. (2000)²²: Sequential patients admitted to the burn center during 1998, which fitted the inclusion criteria. Patients were randomized in control and oxandrolone groups. Randomization was in a double blind pattern – caretakers did not know the groups, only the pharmacists. Criteria for inclusion were:

- Patients with deep burns (2nd and 3rd degree) with 40 to 70% TBSA, including those with inhalation injury and other comorbidities factors and at least 20% TBSA requiring grafting.
- Demling R, DeSanti L. (2003)²³: Patients with large burns whom were transferred to the Brigham and Women's Hospital Burn Center between 1999 and 2001. Patients were randomized in one group receiving physical exercises and optimized nutrition and one group receiving Oxandrolone and physical exercised and optimized nutrition. Patients with prostate or breast cancer history and with elevation of PSA were excluded from the study.
- Wolf SE et al. (2006)²⁴: Multicentric study in 14 Burn Centers. Inclusion criteria: patients of either sex, older than 18, with TBSA equal or greater to 20%. Patients fed orally or through enteral tube up to 5th day after burn and no associated injury (spinal injury, cerebral hypoxia, etc) Exclusion criteria: primary electrical or chemical injury, pregnancy, chronic liver disease, renal failure, cancer, recent or continuous use of steroids or anabolic agents and participation in other studies

Intervention Types

- Demling R. (1999)²¹: Patients randomized in three groups according to criteria in 3.1.2 above, in three groups: Control Group (n=24) without the use of anabolic agents; HGH Group (n=20), with patients using HGH at 0.1 mg/kg, intramuscularly, starting 7 to 10 days post-burn; and Oxandrolone Group (n=16) using Oxandrolone at 20mg/day orally, starting 7 to 10 days post burn. All patients received optimized nutrition primarily based on the basal metabolic rate, according to the method of Wilmore et al.²⁴. After the first week, required calories were adjusted according to indirect calorimetric and respiratory coefficient. Follow up was up to the transfer to a rehabilitation center, with resolution of the metabolic response to trauma, with clean wounds in less than 15% of burn surface area.
- Demling R, Orgill PD. (2000)²²: Patients divided into two randomized groups: Control Group (n=9), with similar characteristics as the index group, using placebo pills containing 150mg of lactulose, corn extract and methyl-cellulose – four pills orally, twice a day, starting 2 to 4 days post burn and Oxandrolone Group (n=11),

four pills, identical as the placebo ones, taken orally twice a day, starting 2 to 4 days post burn. These pills contained 2,5 mg Oxandrolone, 150 mg lactulose, corn extract and methyl cellulose. This regimen totaled 20 mg Oxandrolone per day, which is the dose considered standard in the literature for critically ill patients^{17,18}. Double blind study in which patients were accompanied until transferred to a rehabilitation unit. Transfers occurred when there was no longer a metabolic response to trauma; the wound has been cleaned and with less than 10% total burn surface area (TBSA).

- Demling R, DeSanti L. (2003)²³: Patients with severe burns randomized in two groups: Control Group (n=22) with optimized nutrition and exercises; and Oxandrolone Group (n=23) – defined through inclusion criteria, whom received 20 mg Oxandrolone orally per day, in two dosages and optimized nutrition and exercises. Patients were followed regularly up to six months after no longer using Oxandrolone.
- Wolf SE et al. (2006)²⁴: Patients who fitted the inclusion criteria were placed into groups according to age and % TBSA. In relation to age: 18-44, 45-64 and over 65; in relation to burnt area: 20-30%, 31-40%, 41-50% and 51-60% TBSA. After separating into these criteria, patient were randomized into two groups: Control Group (n=35) who received a pill containing saccharose and the Oxandrolone group (n=46) who received an identical pill in appearance, containing 10mg of Oxandrolone every 12 hours, orally or via tube, starting on the fifth day post burn extending to hospital discharge. Oral or enteral nutrition, surgical procedures for debridement or grafting were offered to all patients according to each institution criteria. Hepatic enzymes were measured when clinically indicated.

Revision Method

Clinical Assay Selection

Clinical assays were selected based in the analyzed data presenting the results of Oxandrolone use. With this aim, two studies were selected which presented enough information for the meta-

analysis. Demling R (1999)²¹ and Demling R, Orgill PD (2000)²². The third study Demling R, DeSanti L (2003)²³ was excluded for not clearly defining the patient with severe burn, and also analyzing gain of body mass in the acute phase instead of loss. In relation to the fourth study, Wolf SE et al. (2006)²⁴, it was not possible to compare its data via meta-analysis, because correspondence with the other studies were only in relation to length of hospital stay, and among the complications, hepatic enzymes analysis.

Data Acquisition and Analysis

Data analysis was performed through meta-analysis using as comparison factors averages, standard deviations and number of individuals in each group of the selected studies.

For data processing, an electronic tool known as “Comprehensive Meta Analysis”²⁶ was used. It is virtually available for tests, correlation coefficient, odds ratio and Fisher Z relation calculations.

All data were displayed in tables and graphs (“florete plot”) for a better results visualization.

Results

Outcomes submitted to Meta-analysis

The analysis of the outcomes in this study, aiming at analyzing the effects of Oxandrolone use in major burn patients, identified the following aspects:

- Donor area healing time
- Nitrogen balance
- Body mass loss
- Side-effects: liver toxicity, androgenic effect- hirsutism
- Metabolic rate
- Length of hospital stay

Meta-analysis results

Data analysis presented in table 1, 2 and 3, and their graphs respectively, demonstrate statistically significant benefits of the use of Oxandrolone, when compared to placebo, in relation to lesser body mass loss, lesser nitrogen loss, and lesser donor area healing time.

When metabolic rate and length of hospital stay are analyzed, there is no statistical difference. Metabolic rate is a normal response to burn injury and there was no difference on its increase between the two groups. Length of stay comparison was hindered because of the small number of patients and the lack of homogeneity amongst the groups.

Table 1/Figure 1 showed through Odds Ratio Log, that the difference among the analyzed factors had significance difference when they are analyzed separately in each study.

Data on Table 2/Figure 2 showed the outcomes significance, through Correlation R meta-analysis, rectifying individual results.

Table 3/Figure 3 presented data comparison through Fisher Z Score, which corresponds to the linear relation among data of different studies.

TABLE 1 - Factors analyzed separately for each study, as body weight loss, nitrogen loss, metabolic rate, wound healing time of donor site and length of stay.

Model	Article	Results	Odds Ratio Logo	Standard Deviation	Confidence Interval	p value	n- Oxandrolone	n- Control	Articler relative weight (fixed)	Article relative weight (random)
	Demling R. (1999)	Body mass lossl (Kg) (1)	3,421	0,699	2,051-4,792	0,000	16	24	12,32	10,37
	Demling R. (1999)	Nitrogen loss (g/day) (2)	5,451	0,845	3,795-7,107	0,000	16	24	8,44	10,01
	Demling R. (1999)	Metabolic rate (%) (3)	-0,684	0,590	-1,841-0,473	0,247	16	24	17,28	10,62
	Demling R. (1999)	Donor Area Healing time (days) (4)	3,628	0,712	2,232-5,023	0,000	16	24	11,88	10,34
	Demling R. (1999)	Length of Stay (5)	-0,210	0,586	-1,359-0,938	0,719	16	24	17,55	10,62
	Demling R, Orgill PD (2000)	Body mass loss (Kg) (6)	3,684	1,033	1,659-5,709	0,000	11	8	5,64	9,48
	Demling R, Orgill PD (2000)	Nitrogen Loss (g/day) (7)	5,459	1,223	3,063-7,855	0,000	11	8	4,03	8,92
	Demling R, Orgill PD (2000)	Metabolic rate(%) (8)	-0,267	0,844	-1,921-1,387	0,752	11	8	8,46	10,01
	Demling R, Orgill PD (2000)	Donor Area Healing Time (days) (9)	2,948	0,969	1,048-4,847	0,002	11	8	6,42	9,67
	Demling R, Orgill PD (2000)	Length of Stay (10)	-1,292	0,868	-2,994-0,411	0,137	11	8	7,99	9,95
Fixed(11)			1,648	0,245	1,167-2,129	0,000				
Random (12)			2,147	0,800	0,579-3,716	0,007				

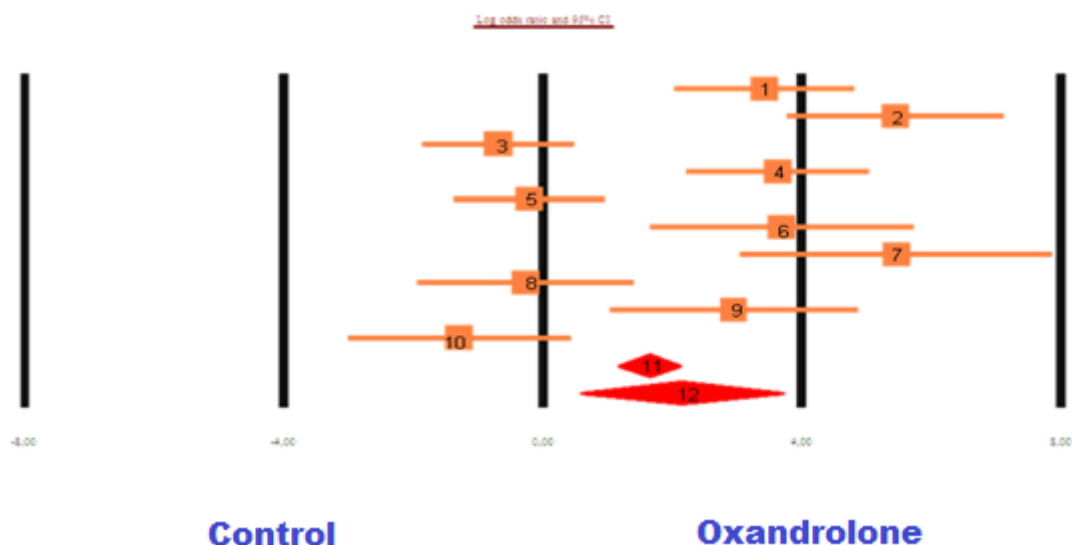


FIGURE 1 - Log Odds Ratio meta-analysis. CI – 95%.

TABLE 2 - Factors analyzed separately in each study for “R” correlation, as body weight loss, nitrogen loss, metabolic rate, cicatrization time of donor site and length of stay.

Model	Article	Results	Correlation	Z value	Confidence Interval	p Value	n- Oxandrolone	n- Control	Article Relative Weight (fixed)	Article Relative Weight (random)
	Demling R. (1999)	Body mass loss (Kg) (1)	0,679	5,959	0,504-0,800	0,000	16	24	14,29	10,38
	Demling R. (1999)	Nitrogen loss(g/day) (2)	0,827	9,196	0,730-0,892	0,000	16	24	16,72	10,47
	Demling R. (1999)	Metabolic Rate (%) (3)	-0,182	-1,171	-0,455-0,123	0,242	16	24	11,19	10,22
	Demling R. (1999)	Donor Area Healing Time (days) (4)	0,700	6,310	0,535-0,813	0,000	16	24	14,57	10,40
	Demling R. (1999)	Length of stay (5)	-0,057	-0,360	-0,351-0,248	0,719	16	24	11,02	10,21
	Demling R, Orgill PD (2000)	Body mass loss (Kg) (6)	0,708	4,449	0,458-0,855	0,000	11	8	6,97	9,78
	Demling R, Orgill PD (2000)	Nitrogen loss(g/day) (7)	0,830	6,389	0,677-0,914	0,000	11	8	7,97	9,92
	Demling R, Orgill PD (2000)	Metabolic Rate Metabolic Rate (%) (8)	-0,072	-0,317	-0,479-0,360	0,751	11	8	5,24	9,43
	Demling R, Orgill PD (2000)	Donor Area Healing Time (days) (9)	0,626	3,570	0,320-0,814	0,000	11	8	6,5	9,70
	Demling R, Orgill PD (2000)	Length of Stay (10)	-0,332	-1,546	-0,654-0,092	0,122	11	8	5,53	9,50
Fixed (11)			0,534	11,364	0,457-0,604	0,000				
Random (12)			0,471	2,770	0,148-0,702	0,006				

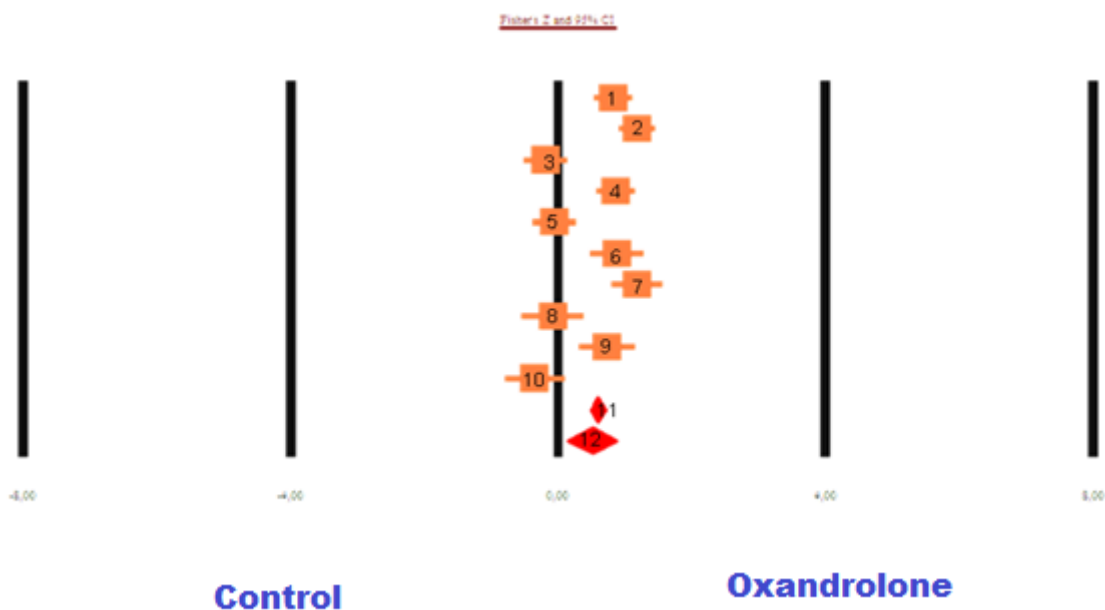


FIGURE 3 – Fisher's Z Score meta-analysis. CI – 95%

Discussion

Major burn patients (over 20%TBSA) represent a great challenge in their care and a great importance to society, when considering the seriousness of their acute phase and the lengthy sequelae treatment period, as well as the treatment cost and difficult physical and social rehabilitation^{1,2}.

As gathered from the literature, it becomes clear that as the percentage of body mass loss increases, so do the complications. A 10% body mass loss will lead to immune dysfunction; 20% to impaired wound healing; 30%, severe infections and 40%, death²⁷. As the catabolism increases, it will also lead to a proportional increase in nitrogen loss.

It is well accepted that a shorter donor area healing time is imperative, since there are few donor areas in major burn patients. Obviously, the faster healing occurs, the faster skin can be re-harvested, and consequently more wounded areas covered.

Major burns will lead to an increase in catabolic rates, leading to lean mass use and decreased protein storage. Lean mass loss will lead to healing and muscle-skeletal impairment⁷⁻¹³. Testosterone analogs have been reported as substances which will lead to a lesser protein loss and to anabolism¹⁴⁻¹⁸.

Results in this study show that the use of Oxandrolone when compared to control (placebo or not) will lead to significant benefits, such as lesser body mass loss, lesser nitrogen loss and lesser donor area healing time.

The question mote for this meta-analysis has been answered in relation to the effects of Oxandrolone on the recovering

of major burn patients. The benefits shown in each study and their results meta-analysis may serve as evidence for the introduction of this treatment in more burn centers which currently are not using it, possibly considering risks, which are not present in this study, in relation to this anabolic agent use.

Conclusion

Clinical Practice Implications

As this study has shown a lesser body mass loss, lesser nitrogen loss and lesser donor area healing time with this anabolic agent, we can suggest the adoption of Oxandrolone use for patients whom present with body mass loss, increase in nitrogen loss or hindered donor area or superficial burn wound healing.

Oxandrolone use in burn centers should be more frequent, in an attempt to create a better critically ill patient management protocol. This could lead to a shorter recovering and rehabilitation time, yielding benefits for the patient and minimize expense on the public health system.

Study Limitations

It must be pointed out that there are only a small number of studies about the use of Oxandrolone in adults. There is a need for new randomized, double blind studies, with a larger number of patients so one could obtain quality evidence. The design should aim at demonstrating a possible shorter hospital stay, a smaller

incidence of complications, such as infection and the consequent use of antibiotics, as well as other factors like a shorter duration of orotracheal intubation.

For this small number of studies, this study showed a meta-analysis of only two articles, even those of a center and conducted by the same investigator, which could adversely affect the results. However, the observance of the articles included in the systematic review, this can damage becomes relative, as all works reveal better patient outcomes with the use of oxandrolone, especially with regard to length of hospital stay endorsed at work multicenter Wolf SE *et al.* (2006)²⁴.

A faster and better rehabilitation of the major burn patient and the optimization of his or her quality of life would be the main goal of these studies.

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