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The Clinical Use of Anabolic Steroid Oxandrolone for Burn Patients: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

To reduce burn damage, especially in severe cases, pharmacological interventions aiming to decrease the intense catabolism such as the use of anabolic androgenic steroids (AAS) have been previously studied. Oxandrolone, an oral derived compound from DHT (dihydrotestosterone), is used since the 60s, was pharmacologically developed to promote a predominance of anabolic action over androgenic action and is also approved by regulatory entities for on-label use in severe weight loss diseases. However, several published studies present differences in their methodologies (e.g. interventional or observational), patients characteristics, oxandrolone doses, usage protocols, clinical outcomes and magnitudes of observed effects. Therefore, we conducted a structured systematic search, in main scientific databases, searching for systematic reviews and meta-analysis that summarized the potential efficacy and safety of oxandrolone use in burn patients. A structured systematic search was carried out using a combination of MeSH terms for

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oxandrolone and burn, filtered for systematic reviews, in PUBMED and CENTRAL database. As a conclusion to the results that we observed (reduction in weight loss and a higher rate of weight regain after burns, a reduction in muscle mass loss, an improvement in muscle nitrogen retention and protein balance, a reduction in the healing time of the donor site, a reduction in the length of hospital stay, an increase in muscle strength, bone mass, total weight gain and growth rate), the clinical oxandrolone use for burn patients can be considered an effective and clinically safe pharmacological intervention and, given the important morphological and metabolic benefits observed in short and long-term, it should be routinely considered as an adjuvant treatment to be added to standard care in burn patients.

Keywords: Queimados; burn; oxandrolone; anabolic steroids.

1. INTRODUCTION

Scientific literature has shown that burn patients often present an increased catabolic state, with associated increase in basal metabolic rate and great loss of lean mass, commonly leading to significant weight loss, muscle mass loss, reduced physical fitness and poor clinical long-term prognosis [1].

Thus, to reduce burn damage, especially in the acute phases of severe cases, pharmacological interventions aiming to decrease the intense catabolism such as the use of anabolic androgenic steroids (AAS) have been previously studied [2].

Among the AAS, oxandrolone is a synthetic oral derived compound from DHT (dihydrotestosterone), used since the 60s, pharmacologically developed to promote a predominance of anabolic action (promoting an increased protein synthesis, and a reduction of protein catabolism) over androgenic action (male secondary sexual characteristics development), approved by regulatory entities for on-label use in marked musculoskeletal catabolism and severe weight loss cases [3].

Several randomized controlled trials (RCT) and observational studies have documented many different benefits of oxandrolone use in burn patients, with improvements on clinical prognosis outcomes [2]. However, it can be clearly seen that they present differences in their methodologies (e.g. interventional or observational), patients characteristics, oxandrolone doses, usage protocols, clinical outcomes and magnitudes of observed effects [2].

Thus, given the positive results shown by previous authors [1-3], may be considered important to summarize studies that have already structured review scientific evidence, such as systematic reviews and meta-analysis, through a broad review of published literature, aiming to translate it into medical practice, the existing knowledge with great potential of clinical applicability.

Therefore, was our objective to conduct a structured systematic search, in main scientific databases, searching for systematic reviews and meta-analysis that summarized the potential efficacy and safety of oxandrolone use in burn patients.

2. MATERIALS AND METHODS

A structured systematic search was carried out using a combination of MeSH terms in English for oxandrolone and burn, filtered for systematic reviews, in PUBMED database (www.pubmed.ncbi.nlm.gov) ("Oxandrolone"[Mesh] OR Oxandrin OR "SC-11585" OR "SC 11585" OR "SC11585" OR Anavar) AND ("Burns"[Mesh]), and CENTRAL database (www.cochranelibrary.com) (#1 MeSH descriptor: [Burns] explode all trees, #2 MeSH descriptor: [Oxandrolone] explode all trees, #1 AND #2). Also, the search was limited to Portuguese, English and Spanish languages, however, with no publication date limit.

3. RESULTS

Two systematic reviews with meta-analysis of data were found (Table 1), observing the effects of oxandrolone use for burns, summarizing the combined clinical results of 1187 patients with intervention (oxandrolone) compared to 2179 patients receiving placebo or standard care [4,5]. Thus, Ring J. et al. [4] found 31 studies (24 RCT, 2 observational and 5 retrospective studies) searching in Pubmed, EMBASE, Web of Science, CINAHL, and CENTRAL. Li H. et al. [5] found 15 RCT searching in PubMed, Medline,

Ovid, Cochrane Library, Elsevier Science, ProQuest, and Springer Link.

The average age of the patients ranged between 6 and 64 years, with 10 to 70% burn extension, at doses ranging from 0.2 mg/kg/day to a maximum of 20 mg/day, administered during the catabolic phase (in-hospital period), rehabilitation phase, and within 1 year after hospital discharge (Table 1) [4,5].

Between several positive results observed by the authors (Table 2) are a reduction in weight loss and a higher rate of weight regain after burns, a reduction in muscle mass loss, an improvement in muscle nitrogen retention and protein balance, a reduction in the healing time of the donor site, a reduction in the length of hospital stay (catabolic and rehabilitation phase), and in the long term (6-12 months), an increase in muscle strength, bone mass, total weight gain and growth rate [4,5].

The authors also evaluated the occurrence of potential adverse effects due to acute and prolonged oxandrolone use, and there was no increase in mortality, infection rate, increased metabolic rate, mechanical ventilation and number of surgeries needed, hyperglycemia or liver dysfunction (Table 2) [4,5].

Furthermore, considering the risk of bias analysis of most of the 39 RCTs analyzed in the two systematic reviews [4,5], the authors described a variation between low or moderate risk of bias, potentially increasing the reliability of the presented information in Table 1 and Table 2.

4. DISCUSSION

Burns are among the most serious traumatic injuries, and the greater the burned body surface, the greater the corresponding increase in metabolic demand (hypermetabolism) and body catabolism (loss of lean mass and body weight) [1,2].

If accentuated hypermetabolism and catabolism are not quickly and sufficiently addressed in clinical treatment of burn patients, especially in the acute phase, greater cardiac and hepatic overload may occur, more clinically significant impairment of muscle function, enhancing the reduction of anabolic hormones, raising infections and sepsis risk, and so, potentially increasing morbidity and mortality rates (not seen as significant results in the present review) [1,2].

Thereby, Li J, et al [5] observed that acute and prolonged oxandrolone use led to a significant reduction in the mean length of hospital stay of 3.02 and 6.45 days, for the catabolic and rehabilitation phases, respectively. Considering the catabolic aspects of burn patients, they also observed an average reduction in weight loss in the catabolic phase (-5 kg), and an average weekly weight gain in the rehabilitation phase of 0.86 kg. Finally, there was a significant associated gain of 5% in lean mass in the rehabilitation phase, adding 3.99% in 6 months, and 10.78% in 12 months, which can provide a better long-term functional prognosis (physical fitness), potentially avoiding sarcopenia and dynapenia [5].

Table 1. Searched systematic reviews and meta-analysis comparative description

Author/year	Databases	Study / patients	Oxandrolone dose	Burn surface
Ring J, et al. 2020	Pubmed, EMBASE, Web of Science, CINAHL, and CENTRAL	Total: 31 (24 RCT, 2 OBS, 5 RETR) 2367 (802 OXA, 1565 PLAC/ STAND)	0.2 mg/kg/day a 20 mg/day	20 a 70%
Li H, et al. 2016	PubMed, Medline, Ovid, Cochrane Library, Elsevier Science, ProQuest, and Springer Link	Total: 15 (RCT) 999 (385 OXA, 614 PLAC/ STAND)	0.2 mg/kg/day a 20 mg/day	10 a 70%

RCT – randomized controlled trial; OBS: observational study, RETR: retrospective study, OXA: oxandrolone, PLAC/STAND: placebo or standard care

Table 2. Comparative primary and secondary outcomes in searched systematic reviews and meta-analysis

Outcome	Ring J, et al (2020)	Li H, et al (2016)
Primary	No effect on mortality (p=0.42) Reduction in hospital stay Mean: -5.75 days; IC 95% (-8.95 to - 2.54) (p<0.01) No effect on hepatic dysfunction (p=0.88)	No effect on mortality (p=0.69) No effect on infection rate (p=0.26) No effect on hepatic dysfunction (p=0.41)
Secondary	No effect on mechanical ventilation days (p=0.75) No effect on transient hepatic dysfunction prevalence (p=0.86) No effect on needed surgeries (p=0.07) Reduction in the healing time of the donor site Mean: -2.75 days; IC 95% (-4.05 to 1.45) (p<0.01) Increase in daily protein balance Mean: +36.61nmol/mL; IC 95% (-0.60 to 73.82) (p=0.05) Weekly gained weight Mean: +0,89 kg/wk.; IC 95% (0.80 to 0.98) (p<0.01) Overall gained weight Mean: +3.09 kg; IC 95% (1.94 to 4.24) (p<0.01) Lean body mass increase Mean: +6.55%; IC 95% (3.30 to 9.81) (p<0.01) Bone mineral density increase (Z-score) Mean: +1.42; IC 95% (0.44 to 2.41) (p<0.01)	*Catabolic phase* Reduction in hospital stay Mean = -3.02 days (-3.66 to -2.37) (p < 0.01) Reduction in the healing time of the donor site Mean = -4.41 days (-5.41 to -3.41) (p < 0.01) Weight loss reduction Mean = -5.00 kg (-6.30 to -3.70) (p < 0.01) Reduction between surgical procedures Mean = -0.63 days (-1.16 to -0.11) (p= 0.02) *Rehabilitation phase* Reduction in hospital stay Mean = -6.45 days (-8.69 to -4.20) (p<0.01) Weekly gained weight Mean = +0.86 kg (0.76 to 0.96) (p= 0.02) Lean body mass increase Mean = +5.00% (3.34 to 6.66) (p<0.01) *Long term* Lean body mass increase *(>6 months)* Mean = +3.99% (3.08 to 4.89) (p<0.01) *(>12 months)* Mean = +10.78% (9.92 to 11.64) (p<0.01)

IC 95%: confidence interval; wk: week

Oxandrolone was one of the first AAS to be administered to burn patients [3] in the acute and in the rehabilitation phase due to its proven property of increasing weight, lean mass, nitrogen balance, without pronounced virilizing (androgenic) effects or high hepatotoxicity (even though it is an oral 17 alpha alkylated AAS), in different diseases that course with accentuated catabolism such as HIV, alcoholic hepatitis, malnutrition, sarcopenia, trauma following major surgery, postmenopausal osteoporosis, spinal cord injury and muscular dystrophies. [6-13].

In agreement with previously published reviews [2,3] about oxandrolone use in this scenario, our present review study with systematic search in main scientific databases, also presented high quality data (2 systematic reviews, with most information coming from RCTs, including more than one thousand burn patients) showing important clinical benefits added to an adequate clinical safety profile, suggesting an idea of a potential first choice drug intervention aiming to reduce hypermetabolism and marked catabolism.

Furthermore, as burns may occur more frequently at younger ages (children and adolescents), benefits of long-term use of oxandrolone, such as bone mass increase, weight gain, muscle mass and height [14,15], also seen in the primary and secondary outcomes analyzed in this study (Table 1 and Table 2), are important to reduce growth impairment and functional consequences during adult life.

Corroborating this, multiple randomized controlled studies including burn children observed positive significant long-term increase in muscle strength (+44.3% ± 13.3%) with oxandrolone treatment (0.1mg/kg, twice daily) [16], greater compared (placebo) weight and height after 18 and 24 months [14,16], and greater bone mineral density in 5-year follow-up [15].

Although some concern about the potential liver toxicity of using an oral 17 alpha alkylated AAS such as oxandrolone has always existed [3], in the present review study we observed that both systematic reviews and meta-analyses [4,5] did not documented a clinically significant increase in hepatic dysfunction incidence in the short or long term, corroborating other previous findings of adequate clinical safety without significant risk of hepatotoxicity [14,15]. However, since there were some cases of slight transient increase in hepatic transaminases, periodic monitoring of this laboratory parameter would be recommended [4].

According to Li H, et al. [5], oxandrolone use was clinically safe without any increase in the mortality, infection, metabolic rate, hyperglycemia, or liver dysfunction. Additionally, as written by the review authors of Ring J, et al. [4], of twelve studies involving 650 patients, four of them reported a total of 9 cases of potential virilization. All presented as clitoral edema in patients with burns in the perineal region, explained as a reflection of the burn edema. Furthermore, no other signs of associated hirsutism were seen, thus making the clinical use of oxandrolone, even in children, relatively safe in not significantly increasing virilization [4].

Akyurek M, et al. (2016) published an article addressing the safety of oxandrolone clinical use in different clinical scenarios, concluding that it is an anabolic steroid with good anabolic potency but without a great increase in risk of important deleterious androgenic effects [17].

Finally, another extremely important factor was the significant reduction in healing time of the donor site (-2.755 to -4.414 days) and the reduction in length of hospital stay (-3.025 to -5.754 days) [4,5], favoring (although not seen as an outcome in the presented systematic reviews) the reduction of overall healthcare costs, generally very high in burn patients [2,3]. According to Anami EHT, et al. [18], would be a comparison between the average daily cost of 1330.48 dollars in a university hospital stay, versus an average cost of 20.2 dollars for the use of 20 mg oxandrolone daily (*www.drugs.com/price-guide/oxandrolone*).

5. CONCLUSION

As summarized in this narrative review, including structured search on PubMed and CENTRAL databases, the average age of the burn patients ranged between 6 and 64 years, with 10 to 70% burn extension, with oxandrolone oral doses ranging from 0.2 mg/kg/day to a maximum of 20 mg/day, administered during the catabolic phase (in-hospital period), rehabilitation phase, and within 1 year after hospital discharge.

Thus, the clinical oxandrolone use for burn patients, as seen in the described results of two recent systematic reviews with meta-analysis of data, can be considered an effective and clinically safe pharmacological intervention and, given the important morphological and metabolic benefits observed in short and long-term, it should be routinely considered as an adjuvant treatment to be added to standard care in burn patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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