Oxandrolone in the treatment of burn injuries:

A systematic review and meta-analysis

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Abstract

Background: Severe burns induce a profound hypermetabolic response, leading to a prolonged state of catabolism associated with organ dysfunction and delay of wound healing. Oxandrolone, a synthetic testosterone analog, may alleviate the hypermetabolic catabolic state thereby decreasing associated morbidity. However, current literature has reported mixed outcomes on complications following Oxandrolone use, specifically liver and lung function. We conducted an updated systematic review and meta-analysis studying the effects of Oxandrolone on mortality, length of hospital stay, progressive liver dysfunction, and nine secondary outcomes.

Methods: We searched Pubmed, EMBASE, Web of Science, CINAHL, and Cochrane Databases of Systematic Reviews and Randomized Controlled Trials. 31 Randomized control trials and observational studies were included. Basic science and animal studies were excluded. Only studies comparing Oxandrolone to standard of care, or placebo, were included.

Results: Oxandrolone did not affect rates of mortality (RR:0.72; 95% CI(0.47-1.08);p=0.11) or progressive liver dysfunction (RR:1.04; 95% CI(0.59-1.85);p=0.88), but did decrease length of stay in-hospital. Oxandrolone significantly increased weight re-gain, bone mineral density, percent lean body mass, and decreased wound healing time for donor graft sites. Oxandrolone did not change the incidence of transient liver dysfunction or mechanical ventilation requirements.

Conclusions: There is evidence to suggest that Oxandrolone is a beneficial adjunct to the acute care of burn patients; shortening hospital stays and improving several growth and wound healing parameters. It does not appear that Oxandrolone increases the risk of progressive or transient liver injury, although monitoring liver enzymes is recommended.

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Keywords: “Oxandrolone”, “meta-analysis”, “mortality”, “pediatric”

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Introduction

Advances in burn care have drastically reduced mortality following severe burns[1-4], and changed the focus of burn research from survival, to how to reduce morbidity and improve long-term quality of life. The change in outcome trajectory initiated a new stream of approaches, such as novel grafting techniques, skin substitutes, critical care bundles, mental health support, and adjuvant drug therapies such as Oxandrolone.

In patients who suffer from severe burn injuries, a substantial inflammatory driven hypermetabolic response ensues. However, the first 48 hours after severe burn injury, known as the 'ebb', or resuscitative phase, are hypometabolic, with decreased cardiac output, metabolic rate, and hyperglycemia[5]. Within 48 hours patients then enter the 'flow', or hypermetabolic state, which may persist for years post-injury[5-7]. The hypermetabolic state is complex and is characterized by a hyperdynamic circulation, excess catecholamine, insulin, and cortisol release, and increased lipolysis which all impair wound healing and graft survival[6-8]. There is also markedly increased insulin resistance (IR) causing profound hyperglycemia and impaired immune function, increasing the rate of infections and further delaying wound healing[7-10]. Loss of both total body weight, whole body protein, and lean body mass from skeletal muscle, defined as hypercatabolic response, contributes to infections, multi-organ failure (MOF), and death[11-14].

In recent decades, systemic steroids such as the androgen analogue Oxandrolone have been used in severely burned patients due to their antagonism of this catabolic state[15-19]. Oxandrolone is an

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orally administered synthetic testosterone derivative which acts primarily as an anabolic androgen, with minimal androgenic activity[19]. Oxandrolone has direct anabolic activity through binding to intracellular androgen receptors (ARs) in skeletal muscle, increasing muscle protein synthesis[19-20]. Oxandrolone has also been shown to have indirect anabolic activity through competitive antagonism of glucocorticoid receptors, decreasing cortisol-medicated muscle catabolism[20]. Wound healing is thought to be improved as a result of increased IGF-1 production, resulting from glucocorticoid antagonism in patients receiving Oxandrolone[20]. Oxandrolone is unique among the currently available anabolic androgens, as it resistant to metabolism by the liver, and therefore may be less likely to induce hepatotoxicity than other androgens[19].

Oxandrolone is FDA approved for the treatment of severe illness, trauma, and muscle wasting disorders. It has previously been shown to improve weight restoration and activity levels in patients with HIV/AIDS-associated myopathy and muscle wasting[21-22], and gain of lean body mass in cachexic patients with chronic obstructive pulmonary disease (COPD)[23]. Oxandrolone has been shown to improve growth, both height and weight, in children with Cystic Fibrosis[24], and successfully improved body composition in neuromuscular disorders such as Deschene's Muscular Dystrophy[25]. In hypermetabolic burn patients, who are both catabolic and have elevated cortisol levels, numerous outcomes such as body composition and hospital length of stay and been improved in studies of patients receiving Oxandrolone[26]. However, individual studies have also demonstrated increased mechanical ventilation requirements and higher rates of transaminitis in patients receiving Oxandrolone, and the current evidence remains conflicting regarding these outcomes[26-27].

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Our review adds to existing literature on Oxandrolone in burns in several ways. First, a meta-analysis including specific outcomes for both adult and pediatric burn patients has not been performed. Given the potential for adverse long-term effects of androgenic agents in children, this is of particular importance. Second, there are conflicting studies regarding potential adverse effects of Oxandrolone use, such as liver dysfunction[28], prolonged mechanical ventilation[29], and delayed wound healing.

Our objective was to complete an updated, comprehensive review of the use of Oxandrolone in both adult and pediatric burn patients. We aimed to assess the effect of Oxandrolone on 1) overall mortality, 2) length of hospital stay, and 3) the incidence of progressive liver dysfunction.

Methods

Literature Search and Study Selection

We searched for published literature, grey literature, and conference abstracts until May 2019 in Pubmed, EMBASE, Web of Science, CINAHL, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. Searched terms were: ("Burns" OR Burn Unit) AND (Androstenedione OR androstane OR oxandrolone OR oxandrin OR anavar OR sc11585 OR sc-11585 OR "17beta-hydroxyl-7-methyl-2-oxa-5alpha-androstan-3-one" OR "17beta-hydroxy-17alpha-methyl-2-oxa-5alpha-androstan-3-one" OR hepandrin OR lonovar OR omnisterin OR oxandrine OR vasorome). Reference lists were scanned for relevant literature.

There was no exclusion based on year or language of publication. Randomized-control trials, prospective, and retrospective observational studies were included. There were no restrictions

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related to age, gender, ethnicity, or mechanism of burn injury of participants. All participants sustained non-superficial burns, involving at minimum 10% of total body surface area (TBSA). Studies which included daily Oxandrolone treatment were included, and studies assessing combined treatment effects of Oxandrolone and another pharmacologic agent were excluded. Unless otherwise specified (Table 1), included studies used a dose 20mg daily for adults and 0.2mg/Kg daily for children under 18 years. Duration of treatment was recorded when available, but no studies were excluded based on the treatment duration. The standard of care, as defined by the institution conducting the study, with no additional pharmacologic interventions was used as the control.

Data Extraction and Quality Assessment

Titles and abstracts were screened by two independent reviewers to identify studies potentially meeting the inclusion criteria. Identified studies were reviewed in full by two members of the review team. Discrepancies were resolved through collaboration with a third reviewer.

Randomized controlled trials were assessed for quality and risk of bias using the Cochrane Collaboration's tool. The GRADE (Grading of Recommendation Assessment, Development and Evaluation) working group definitions were used to grade the risk of bias (Figure 3). Quality of non-randomized studies was assessed using the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) framework[30] (Table 3).

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Outcomes

Primary outcomes were overall mortality, hospital length of stay, and prevalence of clinically significant liver dysfunction. Secondary outcomes included change in bone mineral density, days of mechanical ventilation, overall change in weight (kg), rate of weekly weight gain during the rehabilitative phase, body composition (percent lean body mass), skin graft donor site healing time, net daily protein balance, and total number of surgeries for their initial injury. When more than two studies for each primary and secondary outcome involved only pediatric patients, a separate analysis was conducted for adult and pediatric patients. When varying doses of Oxandrolone were used in the same study, only data from patients receiving standard doses of 20mg/day (adult) or 0.2mg/kg/day (pediatrics) was included. For dichotomous outcomes, studies were not included in the effect-estimates if no event occurred in either group. For primary outcomes, a sub-group analysis with non-randomized studies excluded, to assess if inclusive of these studies impacted the significance of our results.

Data Analysis

All statistical analysis was performed using Review Manager (RevMan) version 5.3. Calculations of risk ratios for dichotomous outcomes was done using the Mantel-Haenszel method for fixed-effects or DerSimonian method for random-effects models. Mean differences were calculated for continuous outcomes. For outcomes with studies containing significant heterogeneity a random-effects model was used, otherwise a fixed-effects model was used. Heterogeneity in effect measures between studies was assessed with the chi-squared test and I^2 statistic. Substantial heterogeneity was defined by an I^2 value greater than 50% or a significant

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chi-squared result. Funnel plots were used to assess for evidence of publication bias. Confidence intervals of 95% and P values were calculated for each outcome. Statistical significance was set to $P<0.05$ for all results.

Results

A total of 671 studies were identified using the pre-defined search strategy (Figure 1). After removal of duplicates, 383 abstracts were scanned and 136 studies were assessed using full-text review (Figure 1). Of these, 31 studies involving 2367 patients were identified for inclusion in the meta-analysis; 802 received Oxandrolone and 1565 received placebo or standard of care (SOC). There were 24 randomized control trials[24-26, 29, 31-47], 2 prospective observational[23, 48], and 5 retrospective observational studies[49-53] (Table 1). 18 studies involved only pediatric patients, defined as under 18 years of age. Year of publication ranged from 1997-2019. 5 studies did not specify the dose of Oxandrolone used. There was no significant difference in age of study participants (mean± SD) between control and Oxandrolone groups (25.0±17.5; 26.5±18.3; p <0.01).

Primary Outcomes

1.1 Overall Mortality

Mortality was included as an outcome in 17 studies involving 1616 patients. An intent-to-treat (ITT) analysis was used, and completion rates were 93% (1057/1137) for controls and 91% (438/479) in the Oxandrolone group. If studies reported mortality rates, the number of randomized participants was used to determine the number of fatalities in each group. There was no significant difference in overall mortality between Oxandrolone and control groups (RR:0.84;

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95% CI, (0.56-1.27); p=0.42) (Figure 2a). Sub-group analysis was performed for the overall mortality in studies only including pediatric patients, less than 18 years of age. This was reported in 7 studies including 987 patients; there was no significant difference in mortality between the Oxandrolone and control groups (RR:1.19; 95% CI (0.67-2.11); p = 0.56). Similarly, mortality for studies involving only adult patients was not significantly different between treatment groups (RR:0.51; 95% CI (0.24-1.08); p=0.08).

1.2 Hospital Length-of-Stay

Hospital length of stay (LOS) was defined as time from admission until discharge to the community or long-term rehabilitation. No distinction was made between time spent in an Intensive Care Unit (ICU), burn units, or standard wards. Hospital LOS was included 11 studies of 1088 patients. LOS was significantly shorter in the Oxandrolone group compared to controls (MD: -5.75 days; 95% CI (-8.95-(-2.54); p<0.01) (Figure 2b). When the 8 studies containing only adult patients and 3 studies on pediatric participants were assessed individually, there remained a significant reduction in hospital LOS for both age groups (Adult: MD:-9.55days; 95% CI(–10.94-(-8.16)); p<0.01, Pediatric: MD:-1.12 days; 95% CI(-1.59-(-0.64)), p<0.01).

1.3 Progressive Liver Dysfunction

Progressive dysfunction was identified as AST/ALT elevation which did not spontaneously resolve (Tuvdendorj[46]), a diagnosis of hepatitis (Thomas[45]), or at least 5 days of AST/ALT levels above 2.5 times the upper limit of normal (Demling[24, 32]). Wolf[47] required an elevation of AST or ALT >100mg/dl. Sixteen studies involving 589 patients reported on progressive liver dysfunction. There was no significant difference in the prevalence of liver dysfunction between

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Oxandrolone and control groups (RR:1.04; 95% CI, (0.59-1.85); p=0.88) (Figure 2c). No irreversible cases of hepatic failure were observed.

Secondary Outcomes

1.4 Mechanical Ventilation Requirements

Two studies of 198 adult patients examined the effect of Oxandrolone on the number of days of mechanical ventilation required. There was no different in mechanical ventilation requirements between Oxandrolone and control groups (MD:0.94 days; 95% CI (-10.05-7.22); p=0.75) (Table 2).

1.5 Transient Liver Dysfunction

Six studies involving 518 patients were included in the analysis of transient liver dysfunction. No studies involved only pediatric patients. The definition of transient liver dysfunction varied between studies, and we included all those which did not require medical intervention for the liver failure or discontinuation of Oxandrolone. Such cases were classified as progressive liver dysfunction (1.3). The definition of transient liver dysfunction used by included studies was most commonly any AST or ALT level above the upper limit of normal (McCullough[51], Murphy[26], Jeschke[28], Reeves[52]). Pham[52] required a serum bilirubin ≥2mg/dl, and Demling[24,31-33] included patients with an elevated alkaline phosphatase level or AST/ALT level above 1.5 times the upper limit of normal. There was no difference in the incidence of transient liver changes between the control and Oxandrolone groups (RR:0.94; 95% CI (0.47-1.86); p=0.86) (Table 2).

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1.6 Number of Surgeries

The number of excision and grafting surgeries during the initial hospitalization of burn patients was compared in 6 studies including 780 patients. There was no significant difference in the total number of surgeries required between Oxandrolone and control groups (MD:-0.97 surgeries 95% CI(-2.01-0.08); p=0.07) (Table 2).

1.7 Skin Graft Donor Site Healing Time

Time (in days) required for skin graft donor sites to heal between excision and grafting procedures was assessed in 7 studies of 597 patients. Though not always described, time to graft healing was assessed in five of seven studies by a trained nurse evaluator who examined donor sites on a daily basis. Days to donor site healing was significantly less in the Oxandrolone group compared to controls (MD:-2.75 days; 95% CI(-4.05-1.45); p<0.01) (Table 2).

1.8 Net Daily Protein Balance

Three studies measured net amino acid production in 72 patients. All patients were less than 18 years of age. Net protein balance was higher in the Oxandrolone group, but not significantly greater than controls (MD:36.61nmol/mL; 95% CI (-0.60-73.82); p=0.05) (Table 2).

1.9 Rate of Weekly Weight Gain

The average weight gained each week in the rehabilitative phase was measured in 6 studies involving 150 patients. None involved only pediatric patients. If rates of weight gain were reported for multiple weeks the average was used, and the standard deviation from the week with the largest deviation was used. Average weight gain per week was significantly greater in the

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Oxandrolone group compared to controls (MD:0.89Kg/week; 95% CI (0.80-0.98); p<0.01) (Table 2).

1.10 Overall Weight Change

Total weight change during the study period was assessed in 9 studies with 214 patients. The final weight of patients in the Oxandrolone group, compared to initial measurements, was significantly higher than in controls (MD:3.09Kg; 95% CI (1.94-4.24); p < 0.01), (Table 2). This was consistent among studies of only adult (MD:4.45Kg; 95% CI (3.79-5.11); p<0.01) and pediatric participants (MD:1.60Kg; 95% CI (1.34-1.85), p<0.01).

1.11 Body Composition

Body composition was measured at admission, and following treatment, in 8 studies involving 194 patients. This information was then used to calculate the change in percent lean body mass (LBM) in both groups. Percent LBM was significantly higher in the Oxandrolone group as compared to the control group (MD:6.55%; 95% CI (3.30-9.81); p<0.01), (Table 2). This finding was consistent in studies involving only adult (MD: 5.36% 95% CI (3.75-6.97); p<0.01) and pediatric patients (MD:1.24, 95% CI (0.90-1.58); p<0.01).

1.12 Bone Mineral Density

Three studies involving 129 paediatric patients compared Bone Mineral Density (BMD), reported as Z-scores, of patients who received Oxandrolone to controls. When multiple BMD measurements were taken only the 6-month post-burn measurement was used, as this was

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reported by all studies. BMD in the Oxandrolone group was significantly greater than in controls (MD:1.42; 95% CI (0.44-2.41); $p<0.01$) (Table 2).

Discussion

Our review showed that Oxandrolone treatment does not appear to effect mortality rates or the prevalence of progressive liver dysfunction, but may decrease length of stay in hospital required for burn patients. These results were consistent in both adult and pediatric populations when analyzed independently. There is evidence to suggest Oxandrolone increases both total and weekly weight gain. Oxandrolone treatment helped preserve lean body mass (LBM), but did not significantly alter net protein balance in skeletal muscle. Bone Mineral density scores were significantly higher for pediatric patients receiving Oxandrolone, an important consideration for considering long-term steroid use in children. Oxandrolone did not affect the total number of excision and grafting surgeries, but decreased time required for graft donor sites to heal, which may in turn lead to faster coverage of deep partial and full-thickness burns and decreased fluids losses. All of these results are indicative that oxandrolone exerts its anabolic effects post-burn thereby reducing the catabolic response.

Several adverse events following treatment with Oxandrolone have been reported in previous studies, the most common being liver dysfunction. Our results are reassuring in this regard, as there was no evidence of higher risk of progressive, or transient liver dysfunction in patients receiving Oxandrolone. However, it should be noted that the minimal level of AST or ALT elevation constituting liver dysfunction (for both transient and progressive definitions) varied between studies (specific criteria used by each study can be found in the Results section). Given

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this, we recommend AST/ALT monitoring in patients receiving Oxandrolone, however concern of hepatic dysfunction does not appear to be a risk which should limit the use of Oxandrolone for most burn patients.

We also assessed the effect of Oxandrolone in patients on mechanical ventilation. Steroid medications may decrease muscle catabolism and improve strength, however they also increase fibrosis and collagen deposition[31]. While this is beneficial for wound healing, it may negatively impact patients during the fibroproliferative phase of acute respiratory distress syndrome, worsening lung function[31]. Our study suggests that is no change in ventilation requirements with Oxandrolone treatment. Another concern with the use of Oxandrolone has been potentially impaired wound healing. Although steroid medications, such as glucocorticoids, are known to cause impaired wound healing[24], pre-clinical studies have demonstrated that Oxandrolone may actually accelerate wound healing by combination of competitive inhibition of glucocorticoid binding sites and the anabolic action of androgens[24]. Our results suggest Oxandrolone does accelerate wound healing, reflected by decreased skin graft donor site healing time.

While not included in the meta-analysis due to insufficient total events, we also reported on virilisation in female patients. Oxandrolone has low androgenic activity, however potential hirsutism in female patients has been of concern. 12 studies involving 650 patients (369 controls; 281 Oxandrolone) explicitly stated if virilisation was observed. Four studies reported 9 possible hirsutism; all presented as clitoral edema in patients with perineal burns, which authors speculated may reflect burn edema. No other virilising effects were seen. All cases reversed following cessation of treatment, untypical of true hirsutism. Based on this review of the

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literature, there is no evidence to suggest limiting Oxandrolone use in children for concerns of virilisation.

Limitations of our study included combining observational and randomized control trials in the meta-analysis. We aimed to minimize this by excluding studies with a lower quality of evidence (case series and case reports). As non-randomized studies may overestimate effect sizes, we assessed all primary outcomes with non-randomized studies excluded, which did not affect the significance of our results (Supplementary Figures 1a-c). There was also variability in how some outcomes (such as liver dysfunction) were reported; in these outcomes we described the various measured used. Quality of Included Studies was assessed using the GRADE working group definitions for RCTs and the ROBINS-I framework for non-randomized studies. Of the 24 randomized studies 14 were of low to moderate risk of bias and 10 were judged to be of moderate to high risk of bias (Figure 3). The majority (4 of 7) non-randomized studies were low-moderate risk of bias, and 2 had at least domains with serious concern for bias (Table 3).

Conclusions

There is evidence to suggest that the addition of Oxandrolone to standard treatment for burn patients decreases length of stay in hospital by accelerating wound healing, but does not appear to affect mortality rates. Although the definition of liver dysfunction was not consistent among the studies included, and we recommend continued monitoring of liver enzymes levels in patients receiving Oxandrolone, we did not find evidence of increased risk of transient or progressive liver dysfunction. Following burn injury, Oxandrolone appears to significantly increase weight gain, accelerate wound healing for skin graft donor sites, and improve body

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composition. We found that children did not experience increased morbidity or mortality when compared adults given Oxandrolone, and may additionally benefit from improved bone mineral density. Therefore, we suggest that Oxandrolone is a safe adjunct in the treatment of severely burned patients.

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Figure Legend

Figure 1	PRISMA flow diagram of study selection. Of 671 articles identified (PubMed (n=225) Embase (n=221) Cochrane (n=74) Web of Science (n=121) CINAHL (n=30)), 31 met inclusion criteria.
Figure 2a	Primary outcomes: overall mortality (relative risk). There was no significant difference in overall mortality between Oxandrolone and control groups (RR:0.84; 95% CI, (0.56-1.27); p=0.42).
Figure 2b	Primary outcomes: length of hospital stay (LOS) in (days). LOS was significantly shorter in the Oxandrolone group compared to controls (MD: -5.75 days; 95% CI(-8.95-(-2.54); p<0.01).
Figure 2c	Primary outcomes: incidence of progressive liver dysfunction. There was no significant difference in the prevalence of liver dysfunction between Oxandrolone and control groups (RR:1.04; 95% CI, (0.59-1.85); p=0.88).

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Figure 3	Risk of bias summary graph of the 24 included randomized studies. 14 studies were low-moderate risk of bias, and 10 were moderate-high risk of bias.

Supplementary Figure Legend

Figure 1a	Mortality of only randomized control trials
Figure 1b	Hospital Length of Stay (days) of only randomized control trials
Figure 1c	Progressive Liver Dysfunction in only randomized control trials

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Table 1: characteristics of included studies

Author, year	Study Design	% TBSA Included	Age (Control)	Age (OX)	Comparator	Treatment (OX)
Capek[48], 2017	Observational (prospective)	53 (mean)			Placebo	Not specified
Hart[23], 2001	Observational (prospective)	20+	7.7	8	Standard of care	0.1mg/kg BID Oxandrolone Start: 6-10 days following first surgery End: after 5 days treatment
Cochran[49], 2013	Observational (retrospective)	15+	45.3	47.5	Standard of care	Not specified
Dobbe[50], 2018	Observational (retrospective)	20+	42.6	40.6	Standard of care	Not specified
McCullough[51], 2007	Observational (retrospective)	10+	40.7	48.8	placebo	10mg Oxandrolone BID Start: Not tracked End: Not tracked
Pham[52], 2008	Observational (retrospective)	20+	42.9	42.3	Standard of care	Oxandrolone (dose not specified) Start: within 7 days of admission End: minimum 7 days, mean 42.9±36
Thorpe[53], 2019	Observational (retrospective)	20+	37	44	Standard of care	10mg Oxandrolone BID Start: Not specified End: 1-10 weeks treatment
Demling[31], 1997	Randomized Control Trial	30-50	34	36	Standard of care + High-protein diet (2 g/kg/day)	10mg Oxandrolone BID Start: Beginning of the rehabilitation phase End: Discharge from rehabilitation
Demling[32], 1999	Randomized Control Trial	25+	40	49	Standard of care	20 mg/day Oxandrolone Start: 10 days post burn End: discharge or transfer
Demling[24], 2000	Randomized Control Trial	40-70	44	49	Placebo	20 mg/day Oxandrolone Start: 2-3 days post-burn End: transfer or discharge (mean 33 +/- 9 days)
Demling[33], 2001	Randomized Control Trial	28 ± 9 (control) 30 ± 10 (OX)	36	37	Standard of care	20 mg/day Oxandrolone Start: Admission End: Not specified
Demling[34], 2001a	Randomized Control Trial	30-55	34	34	Standard of care	10mg Oxandrolone BID Start: beginning of recovery phase End: 4 weeks or until pre-burn weight restored
Demling[34], 2001b	Randomized Control Trial	30-55	60	60	Standard of care	10mg Oxandrolone BID Start: beginning of recovery phase End: 4 weeks or until pre-burn weight restored
Demling[35], 2002a	Randomized Control Trial	<55	32	32	Standard of care	10mg Oxandrolone BID Start: beginning of recovery phase End: 4 weeks or until pre-burn weight restored
Demling[35], 2002b	Randomized Control Trial	<55	64	64	Standard of care	10mg Oxandrolone BID Start: beginning of recovery phase End: 4 weeks or until pre-burn weight restored

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Demling[36], 2003	Randomized Control Trial	37 ± 15 (control) 40 ± 14 (OX)	41	43	Standard of care	20 mg/day Oxandrolone Start: on admission End: when 80% of weight loss was restored
Herndon[37], 2016	Randomized Control Trial	30+	6	6	placebo	0.1mg/kg Oxandrolone BID Start: on discharge End: 1 year post-burn
Jeschke[38], 2007	Randomized Control Trial	40+	7.7	8	placebo	0.1mg/kg Oxandrolone BID Start: 7+ days post-burn End: Discharge from ICU
Murphy[26], 2004	Randomized Control Trial	40+	8.5	8.2	placebo	0.1mg/kg Oxandrolone BID Start: on discharge End: 1 year post-burn
Porro[39], 2012	Randomized Control Trial	30+	8	8	placebo	0.1mg/kg Oxandrolone BID Start: on discharge End: 1 year post-burn
Przkora[40], 2005	Randomized Control Trial	40+	9	9	placebo	0.1mg/kg Oxandrolone BID Start: on discharge End: 1 year post-burn
Przkora[41], 2007a	Randomized Control Trial	40+	11.8	11.8	placebo	0.1mg/kg Oxandrolone BID Start: on discharge End: 1 year post-burn
Przkora[41], 2007b	Randomized Control Trial	40+	10.9	12.1	placebo + exercise regime	0.1mg/kg Oxandrolone BID, Start: on discharge End: 1 year post-burn
Reeves[42], 2016	Randomized Control Trial	30+	7.2	8.6	placebo	0.1mg/kg Oxandrolone BID Start:48 hours after 1st surgery End: 2 years post-injury
Rodriguez[43], 2012	Randomized Control Trial	30+	<19	<19	placebo	Oxandrolone BID (dose and duration unspecified)
Sousse[44], 2013	Randomized Control Trial	60+	±18	±18	placebo	0.1mg/kg Oxandrolone BID Start: Not specified End: 1 year post-injury
Sousse[29], 2016	Randomized Control Trial	30+	13	12	placebo	0.1mg/kg Oxandrolone BID Start: 48 hours post-admission End: 6 months post-injury
Thomas[45], 2003	Randomized Control Trial	40+	7	9	placebo	0.1mg/kg Oxandrolone BID Start: 5 days post-injury End: 1 year post-injury
Tuvdendorj[46], 2011	Randomized Control Trial	40+	7.4	10.4	placebo	0.2mg/kg/d Oxandrolone Start: on admission End: 6 months post-injury
Wolf[25], 2003	Randomized Control Trial	30+	7	8.8	placebo	10mg Oxandrolone BID Start: 5 days post-injury End: Discharge
Wolf[47], 2006	Randomized Control Trial	20-60	40	39	placebo	10mg Oxandrolone BID Start: 5 days post-injury End: Discharge

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Table 2: Secondary Outcomes

Secondary Outcome		Effect	P Value
1.4	Mechanical Ventilation Requirements (days required)	MD:0.94 days 95% CI (-10.05-7.22)	p=0.75
1.5	Prevalence of Transient Liver Dysfunction	RR:0.94 95% CI (0.47-1.86)	p=0.86
1.6	Number of Surgeries Required	RR:0.94 95% CI (0.47-1.86)	p=0.07
1.7	Skin Graft Donor Site Healing Time (days required)	MD: -2.75 days 95% CI(-4.05-1.45)	p<0.01
1.8	Net Daily Protein Balance (mmol/mL in serum)	MD:36.61nmol/mL 95% CI (-0.60-73.82);	p=0.05
1.9	Rate of Weekly Weight Gain (Kg per week)	MD:0.89 Kg/week 95% CI (0.80-0.98)	p<0.01
1.10	Overall Weight Change (Kg)	MD:3.09Kg 95% CI (1.94-4.24)	p<0.01
1.11	Body Composition (percent lean body mass)	MD: 6.55% 95% CI (3.30-9.81)	p<0.01
1.12	Bone Mineral Density (z-score)	MD:1.42 95% CI (0.44-2.41);	p<0.01

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Table 3: Risk of Bias in Non-Randomized Studies

	1)Confounding	2)Selection of Participants	3)Classification of Intervention	4) Deviation from Interventions	5)Incomplete outcome data	6) Measurement bias	7)Selective outcome reporting	Overall
Capek[48], 2017	0	2	2	0	1	1	1	N/A
Dobbe[50], 2018	2	2	1	1	1	1	2	B
Hart[23], 2001	1	1	1	2	1	2	1	B
Cochran[49], 2013	2	3	2	2	2	1	1	C
Thorpe[53], 2019	1	1	1	2	2	1	1	B
McCullough[51], 2007	2	1	1	1	2	2	1	B
Pham[52], 2008	0	2	2	3	1	2	1	C

1=low
2=moderate
3=serious
4=critical
0=unclear

A: low risk for all domains
B: low-moderate risk for all domains
C: serious risk in at least one domain
D: critical risk in at least one domain
N/A: more than one domain unclear, and the study does not appear to be at serious/critical risk of bias

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Figure 1

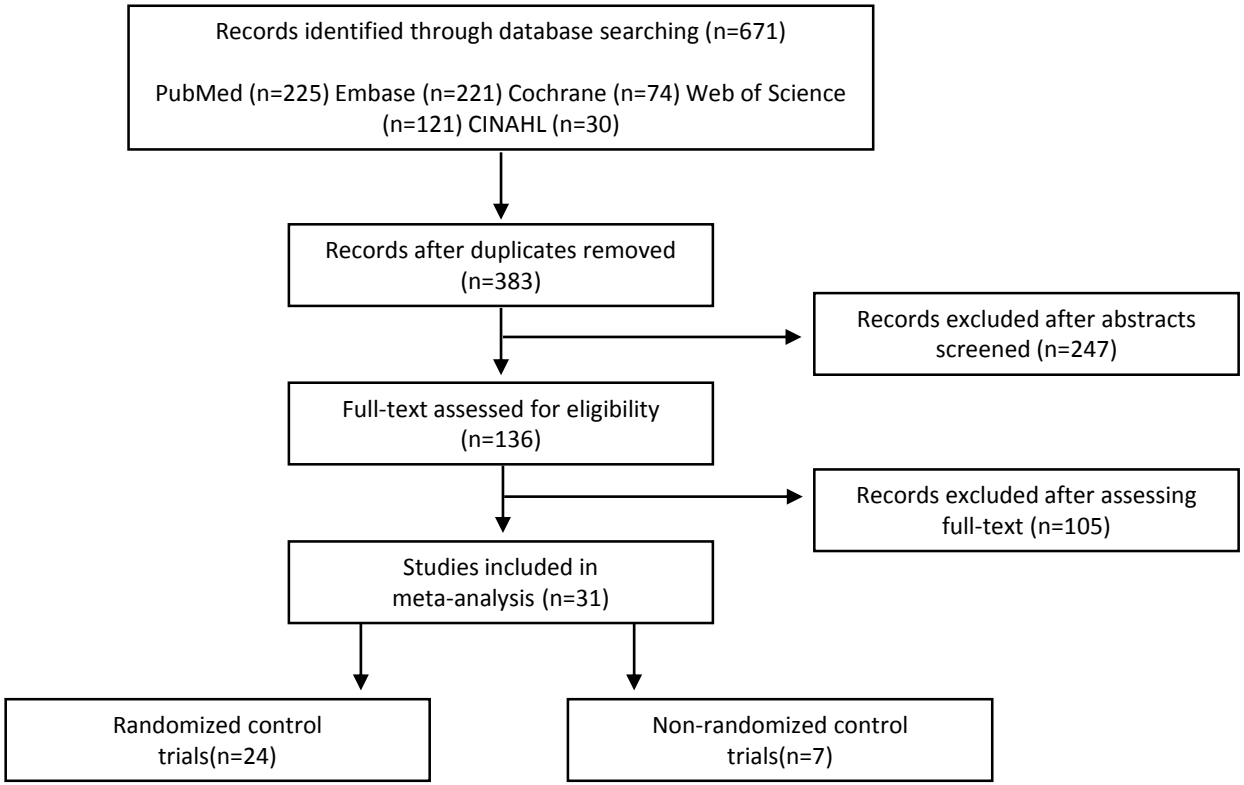

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Figure 2a

Study or Subgroup	Favours [Oxandrolone] Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Capek 2017	0	22	5	172	3.0%	0.68 [0.04, 11.97]
Demling 1997	0	7	0	8		Not estimable
Demling 1999	0	16	0	24		Not estimable
Demling 2000	0	11	0	9		Not estimable
Demling 2002a	0	14	0	14		Not estimable
Demling 2002b	0	11	0	11		Not estimable
Demling 2003	0	23	0	22		Not estimable
Hart 2001	0	7	0	7		Not estimable
Herndon 2016	6	67	9	248	8.9%	2.47 [0.91, 6.69]
Jeschke 2007	4	45	11	190	9.8%	1.54 [0.51, 4.60]
McCullough 2007	2	6	12	61	5.0%	1.69 [0.49, 5.86]
Pham 2008	6	59	16	58	37.6%	0.37 [0.16, 0.88]
Porro 2012	3	70	13	152	19.1%	0.50 [0.15, 1.70]
Przkora 2005	0	30	0	31		Not estimable
Reeves 2016	0	35	3	84	4.9%	0.34 [0.02, 6.36]
Thomas 2003	1	10	0	11	1.1%	3.27 [0.15, 72.23]
Wolf 2006	4	46	4	35	10.6%	0.76 [0.20, 2.83]
Total (95% CI)		**479**		**1137**	**100.0%**	**0.84 [0.56, 1.27]**
Total events	26		73			

Heterogeneity: $Chi^2 = 12.18$, df = 8 (P = 0.14); $I^2 = 34\%$

Test for overall effect: Z = 0.81 (P = 0.42)

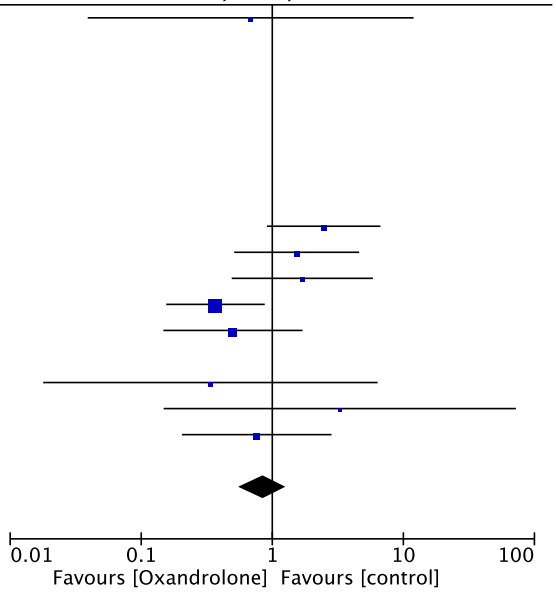

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Figure 2b

Study or Subgroup	Oxandrolone Mean [days]	Oxandrolone SD [days]	Oxandrolone Total	Control Mean [days]	Control SD [days]	Control Total	Weight	Mean Difference IV, Random, 95% CI [days]
Cochran 2013	33.6	15.6	22	43.4	16.9	22	5.7%	−9.80 [−19.41, −0.19]
Demling 1997	22	4	7	26	5	8	9.4%	−4.00 [−8.56, 0.56]
Demling 2000	29	8	11	35	9	9	7.1%	−6.00 [−13.54, 1.54]
Demling 2002a	23	4	14	29	5	14	10.3%	−6.00 [−9.35, −2.65]
Demling 2002b	28	5	11	36	7	11	9.0%	−8.00 [−13.08, −2.92]
Demling 2003	26	6	23	32	8	22	9.8%	−6.00 [−10.15, −1.85]
Dobbe 2018	39.3	22.23	11	42.2	27.2	50	3.2%	−2.90 [−18.05, 12.25]
Herndon 2016	28	3	67	26	1	248	11.6%	2.00 [1.27, 2.73]
Jeschke 2007	28	2	45	31	2	190	11.6%	−3.00 [−3.65, −2.35]
Porro 2012	21.6	3	70	28.5	12	152	11.1%	−6.90 [−8.93, −4.87]
Wolf 2006	32	3.1	46	45.3	5.4	35	11.1%	−13.30 [−15.30, −11.30]
Total (95% CI)			**327**			**761**	**100.0%**	**−5.75 [−8.95, −2.54]**

Heterogeneity: Tau² = 22.97; Chi² = 288.34, df = 10 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.51 (P = 0.0004)

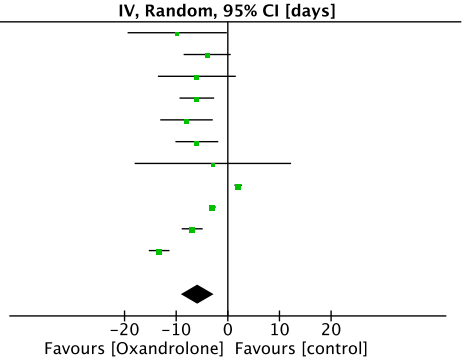

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Figure 2c

Study or Subgroup	Oxandrolone Events	Oxandrolone Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Demling 1999	0	16	0	24		Not estimable
Demling 2000	0	11	0	9		Not estimable
Demling 2001a	0	13	0	17		Not estimable
Demling 2001b	0	8	0	7		Not estimable
Demling 2002a	0	14	0	14		Not estimable
Demling 2002b	0	11	0	11		Not estimable
Hart 2001	0	7	0	7		Not estimable
McCullough 2007	4	6	26	61	67.2%	1.56 [0.83, 2.96]
Murphy 2004	0	42	0	42		Not estimable
Przkora 2005	0	30	0	31		Not estimable
Przkora 2007a	0	9	0	11		Not estimable
Przkora 2007b	0	14	0	17		Not estimable
Thomas 2003	0	10	0	11		Not estimable
Tuvdendorj 2011	0	13	0	10		Not estimable
Wolf 2003	0	14	0	18		Not estimable
Wolf 2006	5	46	2	35	32.8%	1.90 [0.39, 9.23]
Total (95% CI)		**264**		**325**	**100.0%**	**1.67 [0.84, 3.34]**
Total events	9		28			

Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0\%$

Test for overall effect: Z = 1.47 (P = 0.14)

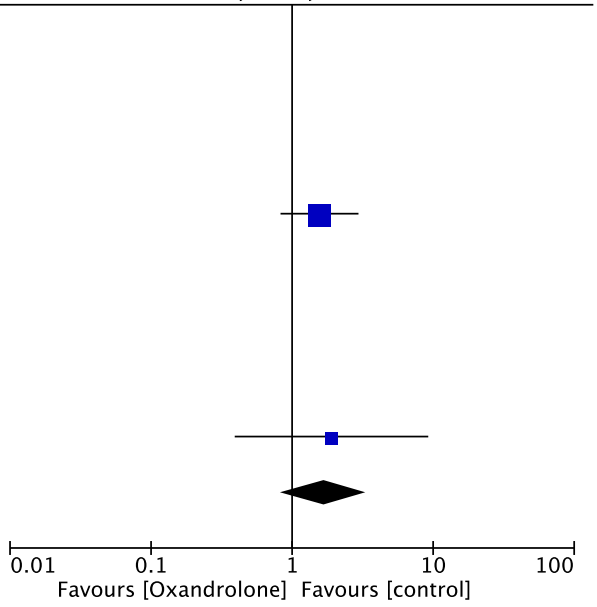

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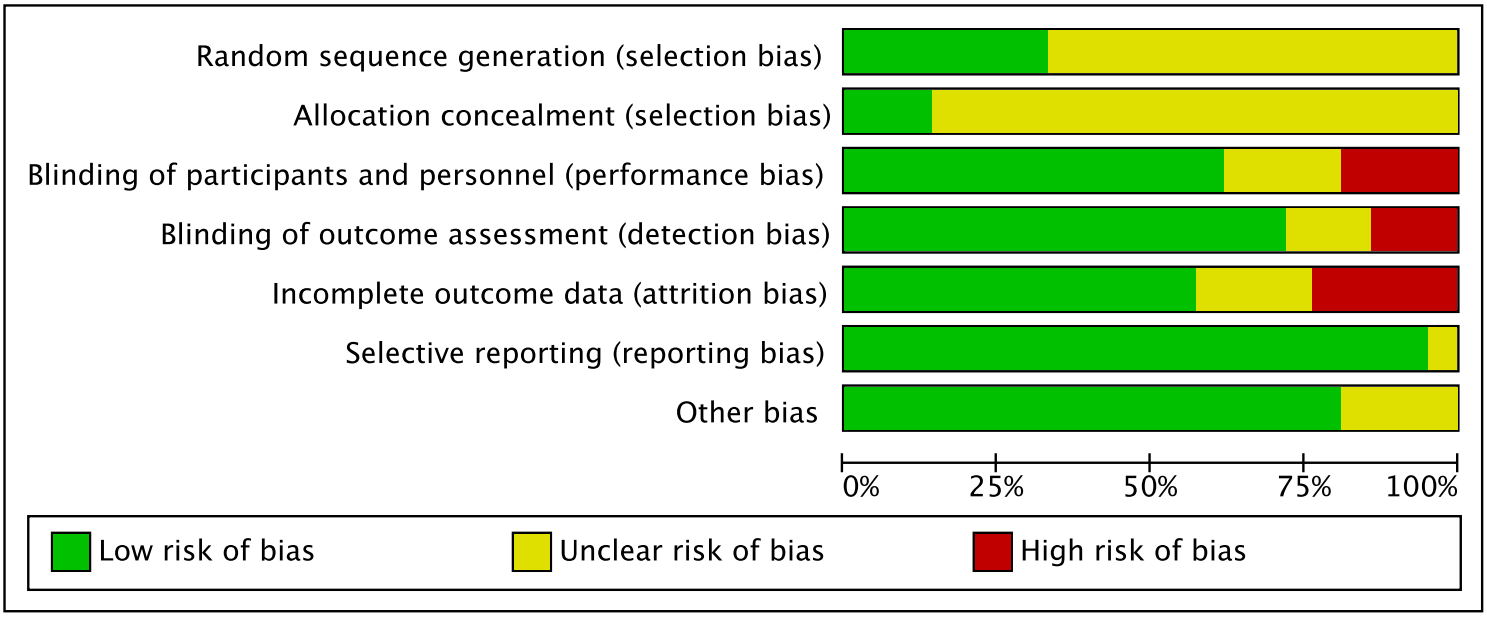
Figure 3



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