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Research Article

Effects of Nandrolone on Outcomes and Metabolic Response in Critically Ill Patients

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ABSTRACT

Background: Two major difficulties in critical care are muscle weakness and malnutrition. Their prevalence in critically ill patients is about 30-50% during hospital stays, and they can also affect routine patient life after discharge, even leading to recurrent infection and death. Metabolic responses to injury have specific effects on metabolic phases in patients.

Methods: This study is a randomized, double-blind, clinical trial on critically ill patients in two groups. Both groups were checked for metabolic markers and demographic characteristics during admission and before discharge. In the nandrolone group, 25mg of nandrolone (IM) was injected weekly for three weeks. In the control group, normal saline was used as a placebo. To assess metabolic responses, albumin, total protein, and testosterone levels were checked, in addition to static measures such as cross-sections of rectus femur and mid-upper arm circumference.

Results: There were no significant differences in SOFA and APACHE 2 scores, PSA, ESR, CRP, and PTC levels between the two groups ($p<0.05$). Results also showed no significant differences between the mean of length of hospital stay, serum albumin, total protein, hemoglobin, testosterone, and HDL between the two groups ($p<0.05$). LDL and TG had P-values of 0.01 and 0.012, respectively. MUAC and sonographic findings of rectus femoris muscle were better in the case group (P-values 0.008 and 0.012).

Conclusion: Nandrolone had no significant effects on metabolic markers in critically ill patients, except for TG and LDL. The changes in muscle characteristics were significant. However, more study is needed to assess muscular power.

Two major difficulties in critical care are muscle weaknesses and malnutrition. Their prevalence in critically ill patients is about 30-50% during hospital stays, and they can also affect routine patient life after discharge [1]. Intensive care unit (ICU)-acquired weakness (ICU-AW) and ICU-acquired diaphragm dysfunction (ICU-DD) are two well-described complications which have been observed in critically ill patients undergoing mechanical ventilation (MV), affecting ICU patients' clinical course and outcomes [2].

The ICU-AW is a multifactorial disorder. It could be due to the drug side effects or the disruption of the microcirculation, indirectly because of muscle atrophy from extended immobilization. Also, catabolic processes contribute to the loss of muscle mass, essentially during the catabolism of myosin, could cause adverse the situation [3]. Metabolic responses to injury have specific effects on all metabolic phases in ill patients. Metabolic responses include a catabolic response in critically ill patients, which is stronger than the same response in starvation since it can result in more obvious inflammatory and stress reactions [4]. These changes manifest as loss of lean body mass (even while receiving nutrition), muscular weakness, tachycardia, and loss of

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energy [5]. Static responses include muscular atrophy, which can affect outcomes, such as increased mortality and length of hospital stay.

Novel treatment procedures have been proposed to limit ICU-AW through initial mobilization of subjects, reducing sedation, and improving nutrition [6-9]. Also, another possible treatment is to provide anabolic support in the recovery stage [7]. Testosterone deficiency is common in critically ill patients [8, 10-11]. This situation may indicate a hormonal imbalance in acute illness. Testosterone therapy in healthy males has been shown to have some advantages on physical functioning, such as developed fat-free mass and muscle strength, but have virilizing side effects for women and negatively impacts cholesterol levels [12-13]. Other anabolic agents like nandrolone and oxandrolone exhibit more impact on muscle strength and have minimum androgenic effects [14].

So, it seems that nandrolone is a practical therapy choice for ICU-AW patients; however, there are a few trials on the effect of nandrolone on the clinical outcomes of these patients. Besides, the underlying mechanisms accounting for the improved clinical outcome are not fully understood.

Methods

This study was designed in the form of a two-way, blinded clinical trial performed on critically ill patients with sepsis, trauma, or after surgery in the ICU. The study cases were selected from critically ill patients with the above etiologies who were admitted to the ICU of Sina Hospital (affiliated to Tehran University of Medical Sciences). Entry criteria included: patient aged between 15 and 80 years (male and female), while exclusion criteria included: renal failure (more than 2 cr); liver disease; pregnancy; coagulation and bleeding disorders; PSA above normal in men; history of anabolic steroids or corticosteroids; a history of neurodegenerative or paralytic diseases; paralysis of the limbs; malignancy; and death.

After the approval of the principles of this study by the Medical Ethics Committee of Tehran University of Medical Sciences, the study cases were selected from among critically ill patients admitted to Sina Hospital ICU, based on inclusion and exclusion criteria, then randomized (using table randomization). Thirty people entered the study in each group, case, and control. In the event of an outbreak, the patient would be excluded from the study. In all patients, the required metabolic markers, albumin, total protein, testosterone, lipid profile, ESR, hemoglobin, and chronic phase reactive proteins (CRP), were measured at baseline. PSA levels were also recorded in men.

Biographic data, including age, sex, weight, and height, were recorded and recorded at the time of entry into and discharge from the ICU. At the time of entry into the study, the patient's condition was recorded based on Apache 2 and SOFA criteria prior to and after Nandrolone injection. Nandrolone initiation criteria were used to improve inflammatory markers, ESR, and CRP, and the patient did not need a vasopressor to improve hemodynamic status. Metabolic criteria, such as albumin, total protein, and testosterone, as well as static criteria, such as the sonographic characteristics of the quadriceps muscle and the size of the arm circumference at the midpoint, were used as criteria to evaluate response to treatment.

By obtaining the criteria for terminating the catabolic phase and initiating the anabolic phase, in the case group, 25 mg Nandrolone (in 1 ml) was injected weekly for a maximum of 3 weeks. In the control group, 1 ml of normal saline was injected weekly for a maximum of 3 weeks. At the same time, for patients, standard nutrition was calculated and prescribed based on the Benedict formula.

The upper arm circumference of the upper midpoint was measured using a standardized non-elastic band instrument with a millimeter accuracy in the upper left arm region (halfway between the acromion process and the ole cranial process).

In terms of measuring the diameter of the quadriceps muscle, the patient was placed on the lower leg with knees fully open so that the tips of the legs are towards the ceiling and the head is not raised or angled during measurement. As a non-invasive, painless technique, ultrasound may be used to identify skeletal muscle pathology. It offers several advantages compared with other tests used to evaluate muscle features and allows for a quick screen of large muscle areas at the bedside (8).

In this case, a non-tensile measuring instrument, such as a linear ruler, is drawn from AIIS to the midpoint of the proximal edge of the patella; the midpoint and one-third between the two reference points are easily accessible. It indicates the rectus femoris. A two-dimensional ultrasound device requires a linear probe (with a frequency of 7-13 MHz) to assess muscle mass to see high-resolution images of shallower buildings. The data collection tool was a two-part questionnaire. The first section included demographic and history specifications, how and why they were referred to the ICU, general patient information at the time of hospitalization, diagnosis, and APACHE II and SOFA scores. Patients were examined for height, weight, sex and age, type of diagnosis, date of admission, APACHE II score for each person, date of death, and cause of death, at the discretion of the treating physician. The second part of the information includes outcome variables such as mortality and length of stay in the ICU and SOFA, and metabolic markers including albumin, total protein, testosterone, lipid profile, and hemoglobin. An example of this questionnaire is attached.

Statistical Analysis

Continuous and categorical variables were presented as mean (SD) and n (%), respectively. To compare the differences between the two groups, we used the student's t-test. A two-sided α of less than 0·05 was regarded statistically significant. Statistical analyses were done using IBM-SPSS version 21.

Results

Demographic findings are shown in (Table 1). There were no significant differences in length of hospital stay, SOFA score, albumin, total protein, Hb, HDL, and testosterone.

Table 1- Demographic findings in cases and controls

	Status	Mean	Std. Deviation
Year	Case	53.4333	20.38032
	Control	51.3000	15.53672
Weight	Case	67.2667	8.01263
	Control	64.7667	11.70229
Height	Case	171.1333	5.74596
	Control	169.1000	7.44798

There were significant differences in triglyceride and LDL and the sonographic characteristics of the rectus femoris and MUAC (Table 2).

Table 2- Statistical analysis of Variables

Variable	P value
Year	0.650
Weight	0.338
Height	0.242
PSA	0.130
Hospitalization_Time	0.920
APACHE	0.191
SOFA_FirstDay	0.752
DeltaSOFA	0.441
DeltaMUAC	0.008
DeltaSonography	0.012
DeltaAlbumin	0.412
DeltaTotalProtein	0.075
DeltaTestosterone	0.918
DeltaTG	0.012
DeltaLDL	0.010

Comparison chart of arm diameter (DeltaMUAC) between two groups of patients was shown in Figure 1. As can be observed, a significant change was detected in the ultrasound survey and arm muscle sizes of the patients.

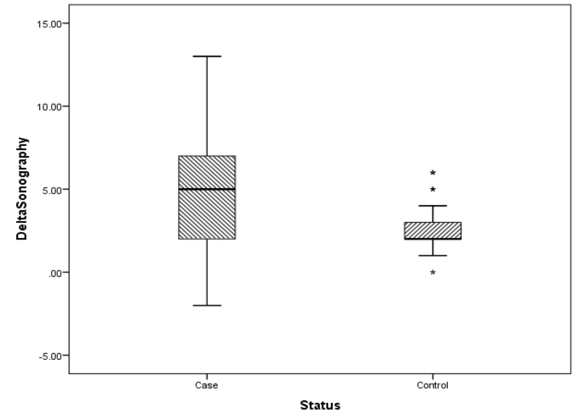

Figure 1- Comparison of the amount of ultrasound changes between the two groups (DeltaSonography).

The direct effects of nandrolone on muscle mass and static characteristics consisting of arm circumference and quadriceps muscle volume has been investigated. In this regard, comparative chart of arm diameter between two groups of patients (DeltaMUAC) has indicated in Figure 2. As a consequence, the overall effects of nandrolone, except for triglycerides and LDL, were not significant for metabolic variables (see Table 2).

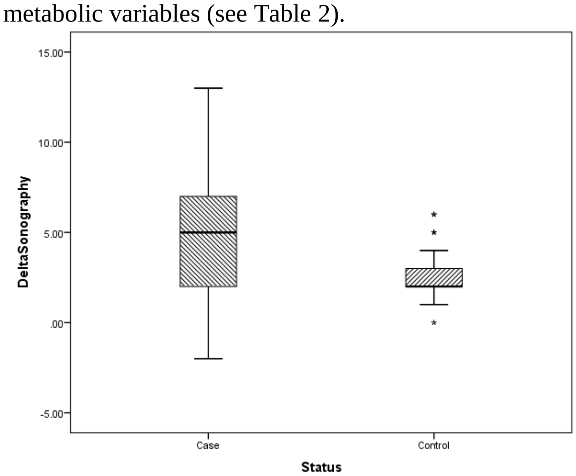

Figure 2- Comparison chart of arm diameter between two groups (DeltaMUAC).

Discussion

One of the most common and important problems in patients in the intensive care unit is atrophy and muscle weakness; we decided to study an anabolic drug, oxandrolone, on mortality, metabolic, and muscle size variables. In this study, we were faced with limitations, including the lack of access to oxandrolone, and we used injectable nandrolone. One of the important things is how to improve muscle size and its performance.

A 2014 paper found it useful to use ultrasound to evaluate response theory and evaluate the success or failure of drug interventions used to help treat muscle atrophy [15].

Real and colleagues noted in a review article published in 2014 in the journal Acta Cirurgica Brasileira that when oxandrolone is used in severely burned adults, it has clear benefits for muscle mass loss. Nitrogen excretion and shorter recovery time were observed in wound healing, compared to a control group [16].

In a 1999 article, Strawford et al. noted that HIV-infected patients with weight loss experienced oxandrolone recovery during their resistance exercise programs [17].

Gervasio et al.'s article entitled "Oxandrolone in Traumatic Patients in 2000" stated that the use of oxandrolone during the first months after multiple traumas showed benefits in clinical prognosis and nutrition [18].

Hausmar et al. published in the Journal of Parenteral and Enteral Nutrition in 1990 that results on the use of Nandrolone and Deconat at 50 mg on the third day and 25 mg on the sixth day stated that anabolic steroids can improve nitrogen balance mainly by reducing nitrogen secretion and that taking nandrolone decanoate increased plasma amino acid levels [19].

Sheffield-Moore et al., in a 1999 paper in the journal Jclin Endocrinea Metab, stated that the major effects of Oxandrolone use in a short period increased muscle protein production in its purest form [20].

Jeschke et al., in an article published in 2007 in the journal Annual Survey, the results of a two-way blind trial study examined the difference in the short-term effects of oxandrolone on burn patients, finding that oxandrolone shortened the length of hospital stay, stabilized LBM, and improved the body's balance of hepatic protein synthesis. It also showed no side effects on the endocrine axis after burns but increased AST and ALT levels [5].

An article published in the Clinical Journal of Nephrology in 2002 states that nandrolone clearly improves markers of nutritional status in dialysis patients [21].

Marttin MF and colleagues, in an article published in the journal Acta Endocrina in 1985, noted that in a study of patients with non-sepsis, body weight and muscle mass were clearly improved following 50 mg of nandrolone per week [22]. As mentioned earlier, sensible changes were shown in the ultrasound survey as well as arm muscle size in our patient (see Figure 1).

In a 2003 study by Pikul and Sharp, the effects of intramuscular nandrolone were tested on 10 patients on a weekly basis for 10 weeks. An amount of 2.5-2 grams per kilogram of body weight per day was determined. All 10 patients responded well to anabolic steroid treatment. The variables tested were pre-albumin, nitrogen balance and muscle mass [23].

In 2007, Jesschke et al. published a study on the results and effects of oxandrolone consumption. Oxandrolone consumption was 0.1 mg per kg body weight for at least 7 days. Also, the levels of complement 3 and alpha 2 macroglobulin, total protein, testosterone, and liver enzymes in the group increased but did not show much difference between the two groups in terms of inflammation and cytokines [5]. ICU-acquired weakness was diagnosed in 130 out of the 344 patients (38%), and was classified as severe in half of them (65 out of 130 patients). The extubation failure rate was 12% (25 out of 214 patients) in patients with no limb muscle weakness, compared with 18% (12 out of 65 patients) in those with moderate limb weakness and 29% (19 out of 65 patients) in those with severe limb weakness ($p = 0.003$ using the chi-squared test and $p = 0.004$ using log-rank test) [24].

Early and proactive rehabilitation of ICU patients is essential to reverse or minimize the impact of ICU-acquired weakness. While ICU clinicians have largely focused on whole-body exercise to address limb muscle weakness (e.g., early mobilization), it is now known that respiratory muscle weakness is twice as prevalent as limb muscle weakness in ICU patients [25]. In our study, several metabolic markers improved after using nandrolone.

Conclusion

Nandrolone is an anabolic drug that has been used for many years to boost muscle-building. In many studies, nandrolone has been used as a stimulant in the anabolic phase in various patients. In the present study, muscle nandrolone was used due to limited access to oral oxandrolone.

In this study, in addition to the effects of nandrolone anabolic and metabolic effects, its effects were studied with regard to hospital stay and mortality, lipid and albumin profiles and protein and hemoglobin, as well as the direct effects of nandrolone on muscle mass and static characteristics (including arm circumference and quadriceps muscle volume) (see Figure 2).

In the results, the effects of nandrolone, except for triglycerides and LDL, were not significant for metabolic variables.

Importantly, in examining the changes in circumference and measuring the ultrasonography of the quadriceps muscle, the findings improved statistically after the Nandrolone injection. Overall, the statistical data in the present study suggest that the use of nandrolone as an anabolic agent in the post-acute phase of critically ill patients admitted to the ICU could have positive results on some metabolic markers and sonographic characteristics of the arm and quadriceps muscles. Whether or not these results are related to improving a person's muscular strength also requires more extensive research.

It is suggested that high protein may help reach better results in metabolic markers. An important consideration, however, remains: Is the improvement in muscular morphology equivalent to better strength, or not?

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