

Effects of anabolic steroid (Oxandrolone) and aquatic strength training in patients with neuromuscular diseases

Efeitos do esteróide anabolizante (Oxandrolona) e do treinamento aquático em pacientes com Doenças Neuromusculares

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ABSTRACT

The objective of this study was evaluated the influence of anabolic steroid (Oxandrolone) in conjunction with loaded aquatic exercises in patients with slowly progressive NMD. Participants were 33: Spinal Muscular Atrophy (n=8), Limb-Girdle Muscular Dystrophy (n=9), Distal Myopathy (n=2), Facioscapulohumeral Dystrophy (n=6), Becker Muscular Dystrophy (n=4) and Myotonic Dystrophy (n=4). The mean age was 33,4 years old.

It was done in four sequential steps of six weeks each: 1) loaded aquatic exercises; 2) oxandrolone (0,1 mg/kg/day); 3) oxandrolone associated with loaded aquatic exercises 4) conventional physiotherapy (without load). The patients were evaluated at baseline and in the end of each step (after 6, 12, 18 and 24 weeks) by the muscular strength test (isokinetic dynamometer (Cybex II), quality of life and "profile of mood states" test.

A statistically significant increased torch peak was demonstrate at 12 weeks in the right knee flexion, 18 weeks in the right elbow flexion, left elbow and knee extension. Statistically significant increased muscular strength was observed only at 18 weeks to left knee flexion and right elbow flexion.

We conclude that oxandrolone in association with loaded aquatic exercises is safe and permits an increased muscular strength even in patients with progressive NMD.

KEYWORDS: anabolic steroids, aquatic exercises, neuromuscular diseases, rehabilitation.

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RESUMO

O objetivo deste estudo foi avaliar a influência do esteróide anabolizante Oxandrolona em conjunto com exercícios aquáticos em piscina aquecida para pacientes com Doenças Neuromusculares de evolução lenta. Foram 33 participantes: Atrofia Muscular Espinhal (n=8), Distrofia Muscular Cintura Membros (n=9), Miopatia Distal (n=2), Distrofia Facioescapuloumeral (n=6), Distrofia Muscular de Becker (n=4) e Distrofia Miotônica (n=4). A média de idade foi de 33,4 anos.

Este foi realizado em etapas sequenciais de seis semanas cada uma: 1) Exercícios aquáticos em piscina aquecida; 2) oxandrolona (0,1 mg/kg/dia); 3) oxandrolona associada a exercícios aquáticos em piscina aquecida 4) fisioterapia convencional 9 sem piscina). Os pacientes foram avaliados antes e após cada etapa (6, 12, 18 e 24 semanas) pelo teste de força muscular (dinamômetro isocinético Cybex II), qualidade de vida, e teste psicológico.

Houve aumento estatisticamente comprovado no pico de torque na flexão de joelho direito na etapa de 12 semanas, e flexão do cotovelo direito e extensão do cotovelo esquerdo e extensão do mesmo em 18 semanas.

Nós concluímos que o oxandrolona em associação com exercícios aquáticos em piscina aquecida permite aumentar a força muscular mesmo que em pacientes com DNM de evolução lenta.

PALAVRAS CHAVE: esteróide anabolizante, exercícios aquáticos, doenças neuromusculares, reabilitação.

INTRODUCTION

Neuromuscular diseases (NMD) are a heterogeneous group of disorders that affects specially the motor unity and usually present a genetic and progressive nature⁹. As there is no definitive treatment to the most of the NMD, a wide rehabilitation program is indicated. Some studies have suggested that loaded physical exercises would be useful to increase the muscular strength in many patients with slowly progressive neuromuscular disorders^{16,17, 19, 20, 29}. The potential benefits and risks of exercise in persons with hereditary NMD has been debated in the literature for many years^{1,13,14}. However, the published study presents many substantial methodological shortcomings, such as too few patients, a large variety of disorders with different etiopathogenic mechanisms, and the absence of a separate no exercising control group having the same conditions.

The dystrophies that involve deficiency or abnormal muscle dystrophin-glicoprotein associated protein, affect the structural integrity of the muscle cell membrane. It is know that eccentric contractions place marked string on the muscle fibers, with

damage evident on ultra structural. The studies in animal models with dystrophy demonstrated greater muscle fibers injury from eccentric contractions compared to controls⁶. Other studies have shown that physical exercises with moderate or high resistance would be useful to increase muscular strenght without damage on the muscle fibers in patients with muscular dystrophies as Myotonic Dystrophy and Facioscapulohumeral Dystrophy^{12, 15, 17, 20, 24, 25, 29}.

In normal individuals a great variation of anabolic steroids has been used to increasing of muscular strenght by inducing the anabolic effect in proteins⁸. Alternatively, with the objective of strength increasing, some authors have used anabolic steroids in some NMD¹⁰, as well as in chronic diseases²⁸.

The objective of this study was to determine whether short-term muscle strength aquatic exercises and the anabolic steroids are efficacious for improving the muscle strength of NMD patients.

METODOLOGY

Thirty three patients with different forms of slowly progressive NMD (mean age 33,4 years old),

on the basis of their clinical picture, electromyography and nerve conduction studies, muscle histology analysis and DNA study, were included in this study. They had the following diagnoses: Spinal Muscular Atrophy(n=8), Limb-Girdle Muscular Dystrophy(n=9), Distal Myopathy(n=2), Facioescapuloumeral Dystrophy(n=6), Becker Muscular Dystrophy(n=4) and Myotonic Dystrophy(n=4). For inclusion, patients had to be ambulatory and maintained ability to flex and extend the elbows and knees fully against gravity.

The procedures were described in detail and a written informed consent was obtained from all subjects. The protocol was submitted to and approved by the institutional ethical Committee of UNIFESP-EPM.

The study protocol was divided in four sequential steps of six weeks each: 1) loaded aquatic exercises; 2) oxandrolone (0,1 mg/kg/day); 3) oxandrolone associated with loaded aquatic exercises; and 4) conventional physical therapy (without load).

The patients were trained twice a week during 45 minutes in steps 1 and 3. The muscle groups exercised were the knee extension (*quadriceps*) and flexion (*isquiotibialis*) and the elbow extension (*triceps braquialis*) and flexion (*biceps braquialis*), bilaterally. The load of 1 kg was fixed to the limb with Velcro. In three patients, we used the load of 0,5 kg due more intense weakness. The patients performed 3 sets of 10 repetitions. The duration of each repetition was approximately 3 seconds. Between repetitions, there was a 3-second rest, and between sets, a 1-minute pause. Patients were instructed how to perform the exercises with weights into the pool and in all sections they were helped by a physical therapist.

Muscle strength of bilateral knee and elbow extension and flexion was measured isokinetically as maximum concentric peak torque and total work by CYBEX II isokinetic dynamometry (Lumex, Bay Shore, New York), according methodology previously described²¹. The measurements were performed at the baseline of the study period (t0) and after 6 (t6),

12 (t12), 18 (t18) and 24 (t24) weeks of follow-up. The same observer took all measurement. Patients were instructed to extend and flex of knee and elbow forcefully and as fast as possible three times in a row. The highest peak torque value of these three movements was used in further calculations.

A questionnaire of quality of life evaluated: social, affection, professional and health) aspects¹⁸. The patients should answer "yes" or "no" for any question, and the final results for any aspects of the study was compared with each others.

We used also the Profile of Mood States (POMS) test that was developed in 1971 by MacNair et al, and adapted by Morgan (1980) for athletic individuals. The agents analyzed were tension-anxiety, depression-dejection, angry-hostility, strength-activity, fatigue-lethargy and mental confusion-bewilderment according to Brandão & Andrade (1997)⁵.

Statistic analysis

In the statistic analysis it was used the Unidimensional Descriptive Analysis, the Parametric Hypothesis Tests and Variance with Repeated Measures techniques (the classification of the techniques can be obtained by "Statistical Theory & Method Abstracts (ISI)").

To the evaluation of the treatment, it as used the Analysis Model of Variance with Repeated Measures²². The repeated measures occur when the observations are taken in different moments for one or more groups, where the subjects have been submitted to some kind of treatment during the study period. For all the tests, it was used the level of significance $\alpha = 5\%$ ($\alpha = 0,05$), so we could reject the hypothesis (parametric hypothesis test) for p-values lower than 0,05 ($p < 0,050$)²².

The patients were divided in two groups (neuropathy and myopathy). They were studied simultaneously during twenty four weeks and had the same performance during this time, without statistically significant. We showed significant increased when patients done the muscular training.

The peak of the torch was demonstrate at 12 weeks in the right knee flexion , at 18 weeks in the right elbow flexion, left elbow extension and knee extension. A statistically significant increased muscular strength was observed only at 18 weeks to left knee flexion and right elbow flexion. These moments corresponded to step with the effect of the oxandrolone isolated (12 weeks) or with loaded aquatic exercises (18 weeks). In the evaluation of the torch peak of the left elbow flexion we observed an ascendant curve with the higher mean at 24 weeks.

Statistical analyses of the quality of life were done with Person's chi-squared test that verified the independence hypothesis among the variables. It showed that the success or failure of the patients were independent of the decisions about the questions of the test⁴.

The Profile of Mood States (POMS) demonstrated that the patients with Spinal muscular Atrophy had smaller average when compared with Myopathies, with statistically significant, especially in the second step.

RESULTS

Muscle strength

Comparing the means of the muscular strength evaluations at the end of each step, there was a statistically significant increasing in torch peak t12($p= 0,008$) to right knee flexion, t18($p= 0,023$ and $p=0,028$) to right elbow flexion and right Knee extension. In relation to the work total, we observed a statistically significant increasing in muscular strength only in t18 ($p=0,013$) to left knee flexion and right elbow flexion. These moments, t12 and t18, were exactly the ones, which the patients were evaluated in the end of each step with the effect of the oxandrolone isolated (t12) or associated to exercises (t18). In the evaluation of the torch peak of the left elbow flexion we observed an ascendant curve with the higher mean at the moment t24. These data are presented at **Tables 1 and 2**.

Table 1: Peak torque (Nm) of patients

Patients	Time	Knee extension		Knee flexion		Elbow extension		Elbow flexion	
		D	E	D	E	D	E	D	E
Myopathy (n=25)	T0	20,8 (34,1)	34,1 (36,6)	25,6 (17,1)	27,8 (18,7)	21,9 (15,3)	20,5 (13,0)	18,6 (15,4)	17,84 (14,49)
	T6	19,4 (36,5)	36,5 (32,2)	28,9 (21,1)	28,4 (20,2)	23,5 (14,3)	22,3 (12,7)	19,6 (13,7)	20,24 (13,12)
	T12	18,4 (34,3)	34,3 (30,5)	30,2 (20,2)	30,5 (20,4)	23,5 (14,9)	24,6 (14,2)	19,9 (13,7)	20,36 (13,09)
	18	20,3 (39,0)	39,0 (35,5)	30,0 (22,2)	31,2 (21,7)	25,6 (16,7)	26,0 (15,6)	22,0 (12,8)	21,08 (13,44)
	24	18,1 (33,4)	33,4 (30,4)	30,2 (21,4)	29,1 (19,6)	24,1 (15,1)	24,6 (14,7)	20,1 (13,7)	21,92 (14,18)
SMA (n=8)	0	18,1 (17,6)	17,6 (20,6)	16,0 (18,7)	13,5 (17,3)	12,0 (8,3)	9,5 (6,2)	10,4 (8,8)	9 6,28)
	6	15,6 (18,9)	18,9 (21,2)	17,1 (19,7)	16,3 (17,0)	12,0 (5,4)	10,9 (6,0)	11,0 (7,4)	10 (5,63)
	12	18,8 (19,4)	19,4 (21,5)	23,1 (25,5)	22,6 (25,7)	12,0 (5,2)	11,6 (5,9)	11,6 (7,7)	11,38 (6,44)
	18	21,0 (20,4)	20,4 (22,7)	17,8 (20,4)	18,5 (19,3)	12,4 (4,4)	12,4 (7,9)	13,3 (7,2)	11,75 (7,87)
	24	18,0 (19,0)	19,0 (20,5)	17,6 (18,4)	17,8 (17,1)	11,0 (5,1)	11,4 (8,1)	12,6 (7,9)	11,25 (6,36)
Total (n=33)	0	20,0 (32,6)	32,6 (35,0)	23,3 (17,7)	24,4 (19,1)	19,52 (14,5)	17,8 (12,6)	16,6 (14,4)	15,7 (13,45)
	6	18,8 (34,7)	34,7 (31,4)	26,0 (21,1)	25,5 (20,0)	20,73 (13,6)	19,6 (12,4)	17,6 (12,9)	17,76 (12,48)
	12	18,6 (33,1)	33,1 (30,1)	28,5 (21,4)	28,6 (21,6)	20,73 (14,0)	21,5 (13,8)	17,9 (12,9)	18,18 (12,37)
	18	20,5 (37,2)	37,2 (34,5)	27,0 (22,1)	28,2 (21,6)	22,39 (15,7)	22,7 (15,2)	19,9 (12,2)	18,82 (12,87)
	24	18,1 (32,4)	32,4 (29,9)	27,1 (21,1)	26,3 (19,4)	20,91 (14,5)	21,4 (14,5)	18,3 (12,8)	19,33 (13,46)

Table 2: Work total torque of patients

Patients	time	Knee extension		Knee flexion		Elbow extension		Elbow flexion	
		D	E	D	E	D	E	D	E
Myopathy (n=25)	T0	31,0 (34,7)	32,5 (35,7)	18,4 (18,0)	18,0 (20,8)	21,2 (19,8)	19,4 (18,7)	16,44 (19,62)	17,36 (20,61)
	T6	30,1 (31,8)	31,0 (30,5)	21,0 (23,9)	19,2 (19,4)	21,1 (19,9)	19,0 (16,5)	17,00 (18,64)	17,56 (16,97)
	T12	30,6 (33,0)	29,1 (30,3)	21,3 (21,2)	19,1 (18,4)	20,3 (20,1)	21,6 (21,1)	15,88 (18,64)	19,04 (19,75)
	18	33,3 (38,7)	32,3 (37,8)	22,5 (22,9)	20,4 (20,3)	22,1 (21,2)	21,8 (22,0)	18,24 (19,91)	19,40 (20,21)
	24	30,3 (32,0)	28,4 (31,0)	21,4 (21,2)	18,0 (18,1)	20,3 (19,1)	19,7 (19,9)	16,32 (18,46)	19,12 (10,18)
SMA (n=8)	0	10,1 (18,7)	12,4 (23,3)	8,8 (17,2)	8,9 (18,1)	9,0 (8,4)	6,5 (8,2)	7,00 (9,06)	5,50 (5,1)
	6	9,8 (17,2)	12,3 (21,0)	10,0 (17,9)	9,3 (15,6)	8,1 (6,4)	6,8 (6,0)	6,38 (7,85)	6,63 (6,1)
	12	9,9 (17,3)	12,3 (22,2)	9,1 (18,1)	10,4 (18,8)	8,8 (7,8)	7,9 (8,3)	8,75 (9,19)	7,00 (6,4)
	18	11,4 (20,3)	13,1 (24,2)	9,5 (20,0)	11,4 (21,0)	8,1 (8,5)	8,5 (10,7)	9,25 (9,57)	7,75 (8,8)
	24	10,4 (18,3)	12,0 (21,4)	8,4 (15,7)	9,9 (18,0)	7,6 (8,4)	7,5 (9,4)	8,25 (9,33)	6,75 (6,8)
Total (n=33)	0	25,8 (32,5)	27,6 (33,9)	16,0 (18,1)	15,8 (20,0)	18,3 (18,4)	16,3 (17,5)	14,15 (17,98)	14,48 (18,7)
	6	25,0 (29,9)	26,5 (29,3)	18,3 (22,8)	16,8 (18,8)	17,9 (18,4)	16,1 (15,5)	14,42 (17,19)	14,91 (15,7)
	12	25,4 (30,9)	25,0 (29,2)	18,3 (20,9)	17,0 (18,6)	17,5 (18,5)	18,3 (19,7)	14,15 (16,99)	16,12 (18,1)
	18	27,8 (36,0)	27,6 (25,6)	19,2 (22,6)	18,2 (20,5)	18,7 (19,7)	18,6 (20,5)	16,06 (18,24)	16,58 (18,7)
	24	25,3 (29,7)	24,5 (29,6)	18,1 (20,6)	16,1 (18,1)	17,2 (17,9)	16,7 (18,6)	14,36 (16,94)	16,12 (18,6)

Quality of life and POMS scales

During the treatment steps it was not observed statistically significant variation in the evaluated quality of life aspects, such as: social ($p=0.959$), affective ($p=0.933$), and professional ($p=1.000$). In health aspect, all have referred failure, not been possible to perform the statistical analysis. In relation to the analyzed POMS variables, we have not observed statistically significant changes during the treatment: Tension ($p=0.309$), depression ($p=0.755$), angry ($p=0.654$), strength ($p=0.367$), fatigue ($p=0.132$) and mental confusion ($p=0.067$).

DISCUSSION

In this study we tested the effects of loaded aquatic exercises and of an anabolic steroid (oxandrolone) in the treatment of NMD patients. The protocol was divided in four sequential steps of 6 weeks each: loaded exercises (step 1), oxandrolone (step 2), loaded exercises and oxandrolone (step 3) and conventional physical therapy (step 4), aiming to evaluate, in a short period of time, isolated physical exercises and oxandrolone and the potentialization of the effects using both at the same time. Our results have shown that at the end of the steps 2 and 3 there was a significantly increasing in torque peak and total work in some of the evaluated muscular groups. No patient showed decreased muscular strength during the study, and no significantly collateral effects were observed with the use of oxandrolone during the three months period of the drug administration.

In this study we have included patients with neuronopathy (Spinal Muscular Atrophy-SMA) and different forms of myopathy (Limb-Girdle Muscular Dystrophy, Distal Myopathy, Facioscapulohumeral Dystrophy, Becker Muscular Dystrophy and Myotonic Dystrophy). We avoided including Duchenne muscular dystrophy, a more rapidly progressive disease, being difficult to evaluate the results of the treatment in a short period of time.

The involved mechanisms in the physiopathology of NMD are very different. In neuro-nopathies as Spinal Muscular Atrophy, there is a fail in the muscle stimuli, occurring muscular atrophy and weakness. We were waiting that, in this group, the effect of the anabolic steroids and the loaded exercises had a better result, once structurally the muscular fibers are normal. Our results have shown that, despite the SMA patients show muscular strength mean better than the myopathic patients, the difference between the means, in both groups, in different steps of the study, was not statistically significant. In this study, it was not possible to evaluate the myopathic patients separately in subgroups, depending on the specific diagnostic, because of the small number of cases.

The evaluation of the efficacy of physical therapy or drug administration is very complex and it involves the interference of various factors. Several methods have been used, and the objective would be to evaluate the capacity of a specific training program to increase the muscle strength, and also to improve the patients' motor function. We used the isokinetic dynamometer because of the strength measurements, especially of isokinetic and isometric knee and elbow torques, are reproducible and give better differentiation of strength than conventional manual muscle testing²¹. Another way, we think that the motor capacities of patients would not change in a short period of protocol.

Classically, these diseases are treated with conventional physical therapy techniques (kinesiotherapy, stretching)³⁰. It is well demonstrated that loaded exercises increase the muscular strength in normal individuals through various adaptive mechanisms of the muscular tissue^{3,7,11}, such as increasing of capillary density, mitochondrial proliferation, and also the protein synthesis. An important question of our study was to set if these changes would be able to increase the muscular strength in NMD patients.

According to Vignos, 1983, patients with NMD can be benefited with the performance of loaded exercises, since they avoid the muscular

fatigue. All of the loaded exercises and NMD studies were performed on the ground. There is, in consulted literature, no study verifying the efficacy of loaded aquatic exercises. The physical properties of the water as empuxo, floating and other forms, facilitate the performance of the exercises^{3, 26}. In this study, it was performed tests with loads of 0,5 Kg or 1,0 Kg, according to the maximal resistance of each patient. The chosen muscles are exactly the ones we consider important to perform the most of functional abilities, such as, quadriceps, isquiotibialis, biceps braquialis and triceps braquialis.

Our study have shown that, comparing the evaluation of the steps, there was a statistically significant increasing in torch peak in t12 to right knee flexion, t18 to right elbow flexion and right Knee extension. In relation to the work total, we observed a statistically significant increasing in muscular strength only in the moment t18 to left knee flexion and right elbow flexion. These moments, t12 and t18, were exactly the ones, which the patients were evaluated in the end of each step with the effect of the oxandrolone isolated (t12) or associated to exercises (t18). In the evaluation of the torch peak of the left elbow flexion we observed an ascendant curve with the higher mean in t24.

We also observed that when we compare the beginning and the end of the treatment (24 weeks) it was observed statistically significance only in the evaluation of torque peak of right knee. In the other cases there was a decreasing on the mean muscular strength in the last evaluation (24 weeks), when the patients performed only conventional physiotherapy without load, showing, in these cases, the absence of statistic significance when we compare the beginning and the end of the treatment. It is important to consider that the objective of the study was not to compare the muscular strength between the beginning and the end of the treatment, but among the different steps.

The decreasing of the evaluation means in the end of the 24 weeks observed in the most of the tested muscular groups can have diverse explanations. The fact that they are no longer using

neither medication nor loaded aquatic exercises can have provoked some disappointing in patients in the last evaluation. Nevertheless, the absence of muscular stimulus produced by the exercises and oxandrolone must be the most probable factors. It is important to say that neither case showed a worsening of the muscular strength in the last step in relation to the beginning of the treatment, especially considering the fact that we are working with progressive diseases.

The use of a control group certainly would be of great value to help us in the interpretation of the findings. We have not used a control group in this study because we would need an enormous patient group, and we would have to leave a part of them without treatment, what is not indicated, once the diseases are very severe. Further studies with wider patient groups may help us on obtaining more definitive conclusions.

In our study we have exercised both body sides of the patients. Our intention was to evaluate the muscular strength independently of the dominant side. Previous studies demonstrated that there was not a significant difference in the response of the exercised and no exercised sides, although the exercised side generally tended to show greater improvement². Curiously the studies that exercised only one side have demonstrated muscle strength increase also in the no exercised side^{2,19}. These authors suggested that neural rather than muscular adaptations were the likely cause of observed strength increases in the no exercised limb¹⁹. However, that increases in strength in a no exercised limb were not associated with any changes in muscle size, muscle fiber size, or evoked contraction strength²⁷.

A great variation of answers to anabolic steroids has been reported, and related to the increasing of muscular mass and strength in normal individuals and athletes, by inducing anabolic effects by androgenic receptors, and also inhibiting the protein catabolism via glucocorticoids receptors^{24,31}. The testosterone stimulates the muscular hypertrophy via its affects in somatomedine, influencing the

increasing of the size of muscle fiber. Nevertheless, trustable reports about the effects of the anabolic steroids have been difficult to obtain. In the performed studies, we can verify the use of many diverse doses and variable methods of administration, and relatively short periods of sequences.

Oxandrolone was the chosen anabolic steroid in our study because of it is administrated orally. Moreover, it has already been used in other studies with patients with NMD, without significant adverse effects^{23,28}. We used a dose of 0.1mg/Kg/day, previously tested in Duchenne patients, who promoted a stabilization of the muscular strength during treatment¹⁰, and in low stature children, promoting growing acceleration³¹, without significant adverse effects. In other situations, such as HIV patients and athletes, it has been used greater doses, showing significant increasing of muscular strength²⁸.

We observed that using 0.1 mg/kg/day, during 12 weeks, oxandrolone showed safety, not presenting any secondary effect that would indicate an interruption of the drug use. The systemic effects that could appear as voice changing, acne, and aggressiveness were not observed. Nevertheless, there are no studies on literature evaluating the effects of anabolic steroids in patients with NMD during a large period, not being possible, so, to determine the benefits or adverse effects of these medication in long-term.

The evidence, by the patient, of a genetic degenerative disease, without a definitive cure and with progressive motor limitations is psychosocially devastating. The opposite, when the patient is called to participate in a research protocol with drugs, certainly the positive expectative is going to be great, leading to a positive step on quality of life. A decreasing in some quality of life items or changes on the states of mood during the study could negatively interfere on exercises and muscular strength tests performance. The evaluation used in our study has shown that there was no significant difference on quality of life that could interfere on

the performance of the exercises and muscular strength tests.

The POMS was used in all of the steps of this study. In general, the patients have manifested an increasing pattern of mood state, especially on the second step of the study, when they were medicated. Although, in short-term studies, it becomes difficult to separate if the mood pattern have increased either because of the real increasing of the muscular strength or because of a positive psychological effect. However, the comparison between the means during the treatment was not statistically significant, showing an absence of significant variations of the mood state during the diverse steps of the study.

CONCLUSION

We conclude that the use of oxandrolone, especially in association with loaded aquatic exercises, during a short period, is safe and permits attend a maintenance and/or an increased muscular strength in patients with progressive NMD.

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