RESEARCH ARTICLE

Comparison of Deflazacort and Prednisone in Duchenne Muscular Dystrophy

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Parvaneh KARIMZADEH MD[1]
Ahad GHAZAVI MD[2]

Abstract

Objective

Duchenne muscular dystrophy (DMD) is a degenerative disease that usually becomes clinically detectable in childhood as progressive proximal weakness. No cure is yet available for DMD, but the use of steroids improves muscle strength and function. This study has been carried out to select the best steroid for the management of DMD.

Materials & Methods

This study is a single-blind, randomized clinical trial with a sample volume of 34 DMD patients. Half of these patients were treated with deflazacort (0.9 mg/kg daily) and the other half with prednisone (0.75 mg/kg daily) for a period of 18 months. The motor function score and excess body weight were registered one year after the start and also at the end of the study and compared between the two groups.

Results

Deflazacort was more effective in the improvement of motor function after one year, but there was no significant difference between the two drugs at the end of the study (18 months after start). Weight gain after one year and at the end of the study was higher in prednisone group and steroid treatment with deflazacort appears to cause fewer side effects than prednisone regarding weight gain.

Conclusion

Deflazacort seems to be more effective than prednisone in the improvement of motor function causing fewer side effects, particularly weight gain. This medication may be important for the improvement of motor function and could be used as the best steroidal treatment for Duchenne muscular dystrophy.

Keywords: Duchenne muscular dystrophy; Deflazacort; Prednisone

1.Associate Professor, Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2.Assistant Professor, Pediatric Neurology Research Center, Urmia University of Medical Sciences, Urmia, Iran

Corresponding Author:
Ghazavi A. MD
Email: ghazavi.ahad@gmail.com

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Introduction

In 1868, Guilaume Duchenne, a French physician living in Paris defined a pseudohypertrophic paralysis showing a muscular appearance in the extremities (1-3). Duchenne muscular dystrophy is an X-linked form of muscular dystrophy involving cardiac and skeletal muscles (4-6). The prevalence is 1/3500 in boys, but it may involve females with Turner's syndrome too (XO) (1,4,5). The responsible gene was identified in 1987. It is located on the short arm of the X chromosome and it codes for the protein dystrophin which is responsible for the stability of the cellular basement membrane (4,5,7). Muscular fibers without dystrophin are very sensitive to mechanical contraction. This defect is the cause of muscle fiber death

finally leading to replacement by fibrous connective tissue (4,5,7).

Duchenne dystrophy patients suffer from a progressive predictable muscular weakening. Most of the patients lose their ability to move when they are 6 to 12 years old (1,4,5). Cardio-respiratory failure and scoliosis occur gradually (4,5).

Many treatment plans such as basic cell and myoblast transfer, replacement or repair of the problematic cell and drug therapy are under research (1,6,8,9). Steroids have shown advantages in retaining muscular function, such as increasing the muscular bulk and diminishing the muscular degeneration speed, but are associated with severe alternative complications (4,7). Prednisone was first used, then a newer steroid called deflazacort which is an oxalone extract of prednisone was experimented and the numerous studies showed that this medicine is as competent as prednisone in retaining muscular function with fewer complications (4,6,10-12). The objective of this study was to compare the advantages and disadvantages of deflazacort and prednisone in the treatment of Duchenne muscular dystrophy. The results of this study may be used to select a more appropriate and more effective treatment method.

Materials & Methods

In this study, all patients with the 5 below diagnostic criteria for Duchenne dystrophy were enrolled:

-Muscular weakness below the age of 5 years

-Male gender

-Proximal muscle weakness

-An increase of more than 40 fold the normal limit of CK in the beginning of the symptoms

-Confirmation of the diagnosis by:

a) Muscle biopsy to prove dystrophin deficiency or

b) Genetic evaluation to confirm dystrophin gene deletion

After enrollment, according to the above criteria, the patients were randomly placed on one of the following mentioned protocols; 0.75 mg/kg/single dose/day prednisone as 50 mg tablets and in case any complications occurred this dose was decreased to 0.3 mg/kg and if there still were complications, the drug was discontinued and the patient was excluded from the study; 0.9 mg/kg/single dose/day deflazacort and in case any complications occurred this dose was decreased to 0.5 mg/kg and if the complications were uncontrollable with this dose the patient was excluded from the study.

The patients were examined at the beginning and also in between the study as mentioned below for the following mentioned functions:

Every 3 months for movement function using the below modalities and grading in three levels for each modality, in which increase in each modality demonstrates worsening of the muscular function. These modalities were:

A. Going up four 17 cm stairs

B. Getting up from the sitting position to the standing position

C. Walking 10 meters on flat ground

Grading:

Grade 1: Accomplishing the task without assistance

Grade 2: Accomplishing the task with assistance

Grade 3: Not being able to accomplish the task

It is necessary to mention the fact that movement ability was evaluated in every visit.

- Measurement of height and comparing it with the height at the beginning of the study every 3 months according to the children's standard height growth chart. Considered abnormal in case of no increase based on the height percentile at the beginning of the study.
- Measurement of weight every 3 months.
- Measurement of blood pressure every 3 months and comparing it with the standard blood pressure chart for children.
- Annual ophthalmic evaluation for cataract.
- Annual orthopedic evaluation for scoliosis and in case of a higher than 20 degree increase, sending the patient for repairment surgery.
- Checking for glucosuria every 3 months.
- Recommendations to prevent weight gain in every visit for a 3-month-period and introducing the patient to a nutrition specialist in case of 5% to 10% increase in weight.
- Annual spirometry and vital lung capacity as an index for respiratory function by a child respiratory subspecialist. A vital lung capacity of less than 80% normal based on the patient's age and gender was considered as abnormal (13).
- Annual referral to a child cardiac subspecialist for

measurement of ejection fraction as an index for cardiac function. An ejection fraction less than 55% normal based on the patient's age and gender was considered abnormal.

For the patients enrolled into the study, 500 mg calcium and 400 IU vitamin D was prescribed in addition to steroid.

Statistical Analysis

SPSS 17 for Windows (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Comparison between groups for quantitative variables was carried out by the T-test or nonparametric equivalent test and for qualitative variables the Chi-square test was used. This study was confirmed by the ethical committee of Shahid Beheshti University of Medical Sciences and written consent was obtained from the parents of children who were enrolled into the study.

Results

This study was performed to compare the effect of deflazacort and prednisone in the treatment of Duchenne muscular dystrophy. Thirty-four Duchenne muscular dystrophy patients based on the inclusion criteria were enrolled into the study from 23rd of September 2008 to 21st of March 2009. The patients were treated alternatively by prednisone or deflazacort; prednisone was prescribed for 17 patients and deflazacort was prescribed for 17 patients with the dose mentioned previously.

Eight of the patients were excluded from the study for different reasons. The advantages and probable side effects of the medications were explained completely for the children's parents together with Duchenne muscular dystrophy, the treatments available and the outcome of this disabling disease. Nevertheless, some of the parents changed their minds, maybe because of the threat of steroid treatment and the side effects that are mentioned by some people and also some physicians. Another cause for the parents' give-up after a few weeks that happened for four of the children was the immediate response to treatment the parents expected despite the complete given explanation regarding this matter, which may be due to the false broadcasting by media or sites on the internet introducing medications that promise complete cure for this disease. These have no scientific base and have no intention other than to empty people's pockets. Of these eight cases who did not continue therapy, three were on deflazacort and five on prednisone medication. This study was continued with 26 cases, of which 14 were patients using deflazacort and 12 were patients using prednisone. These patients were followed up for 18 months till March 21, 2009 and in every visit everything was carried out according to the study method.

The mean age of the patients in the deflazacort group was 7.1±1.98 years (range, 3.2-10.5) and for patients on prednisone medication this figure was 7.37±1.27 years (range, 6-10). In this study, after one year and also after 18 months the mean of motor function index and the mean weight was calculated and recorded for each patient and the two groups were compared regarding these factors at that time. We have to mention that the motor function index has a 9 grade score based on the ability to get up from the ground, walking on flat ground for 10 meters and going up four steps with the height of 17 cm each. Based on the method mentioned before, score 1 indicates the ability to work without assistance, score 3 indicates inability to perform. Therefore, 9 is the worst and 3 is the best motor function index. The increase or decrease in this index compared with the beginning of the study which demonstrates worsening or improvement of the movement function was calculated for each patient for both follow-ups separately and the mean of these percentages were compared between the two groups.

One year after the study started, the mean of this percentage for deflazacort group was 14.99% ±11.19% (range, 0%-40%) compared with the beginning of treatment showing improvement in motor function in this group (as a result of decrease in the motor function index). The mean percentage of this index for the prednisone group at this time compared with the beginning of therapy was 18.07%±5.2% (range, 20%-25%).

With the use of paired t-test, comparison of these two showed that there is a significant difference between them (p=0.001) and deflazacort has a better role in motor function than prednisone (Table 3).

After one year from the beginning of the study, the percentage of weight increase compared with the weight before therapy in the deflazacort group was

12.95%±9.24% (range, 2.08%-29.41%). This figure was 21.65%±6.68% (range, 10%-30%) for the prednisone group (Table 3).

There was a significant difference between the mean weight before therapy and one year after therapy between these two groups (p=0.001) and this points to a higher increase in weight in the prednisone group. We have to mention that all the patients under prednisone treatment and some of the patients under deflazacort treatment had a 5% increase in weight and were subsequently introduced to the nutrition consultant for weight control and were subsequently given advice. Therefore, in the prednisone group the dose of prednisone was decreased from 0.75 mg/kg to 0.3 mg/kg for all the patients throughout a one-year process, but in the deflazacort group the decrease was from 0.9 mg/kg to 0.6 mg/kg in only three patients.

One year after the study started, four patients from the prednisone group were excluded from the study as a result of uncontrollable weight increase despite nutrition consultation. These four patients also had motor function reduction and the parents did not accept change to deflazacort and continuation of the therapy.

Therefore, the last 6 months of the study was continued with 14 patients in the deflazacort group and eight patients in the prednisone group.

After the study was finished (18 months after the beginning of the study), the mean of motor function index compared with the beginning of the study was 24.46%±4.52% (range, 40%-60%) for the deflazacort group and 29.24%±14.79% (range, 20%-60%) showing improvement in motor function in deflazacort group patients (Table 3). According to the paired t test no significant difference was detected between these two groups (p=0.128) demonstrating the fact that none of these medications have advantages over the other. Maybe the reason for better results for deflazacort was because after one year four patients from the prednisone group were excluded from the study as a result of uncontrollable weight gain and these were the patients who had worsening of motor function compared with the beginning of the study and the eight patients who continued the study had a better motor function state.

At this time, the mean weight gain compared with the start of this study in the deflazacort group and the prednisone group was 21.67%±11.96% (range, 4.17%±44.12%) and 32.04%±8.88% (range, 17.5%-45%), respectively, expressing no significant difference statistically between the two groups (p=0.046) and a higher increase in weight using prednisone (Table 3).

In this study, the patients' blood pressure and height was measured every 3 months revealing no increase in blood pressure in any of the groups according to the age-specific standard curve.

In the deflazacort group, the patients' mean height was 116.6±11.65 cm between the 25% to 50% percentile according to age, which was 122.06±9.05 cm for the prednisone group. This index was 123.39±12.20 and 128.31±8.8 for deflazacort and prednisone, respectively at the end of the study for the same percentiles presenting an appropriate growth in height in both groups. Of course, in order to compare the drug effects on blood pressure and height growth a more prolonged study is necessary.

Other evaluations regarding this study that have been carried out annually were the evaluation of the vital respiratory capacity, of which a less than 80% normal based on age and gender was considered abnormal (13) showing a decrease in the respiratory function, in which none of the groups had an abnormal vital capacity throughout the study.

In addition, no cardiomyopathy was observed in the patients based on the decrease in ejection fraction (the normal EF was considered as 55% above normal in echocardiography. This index was always measured by a confirmed pediatric cardiology subspecialist). There was also no cataract observed in the annual follow-up.

In the spinal column evaluation, there was no scoliosis. Apart from one patient in the deflazacort group who had a 10 percent scoliosis in the beginning of the study and was introduced to an orthopedic specialist for a brace and had no increase in scoliosis in the follow-up, there was no other scoliosis detected.

There was no positive urinalysis for glucosuria in any of the groups in the 3-month evaluation.

Complications such as cardiomyopathy, decrease in respiratory function and scoliosis are usually seen in Duchenne muscular dystrophy when the patient reaches a higher age and is unable to move and the patients in this study have a mean age of 7, too soon for these problems. All the patients were able to walk and none needed a

wheelchair. Although none of the two groups had such difficulties, comparison between these two groups regarding the side effects needs a prolonged study that will be followed up in these patients.

In order to find out whether there is any correlation between the weight gain after medication and motor function reduction, Pearson test (r=0.665) was used and one-year after medication there was a significant correlation between the two indices ($p<0.001$) which shows that the possible reason why deflazacort was better than prednisone in the improvement of motor function after one year was less weight gain in the deflazacort group. Maybe it would be feasible to control weight gain when the patient is under prednisone therapy by following nutritional advice; therefore, these two drugs may have similar impact leading to prescription of prednisone instead of deflazacort in patients who can not use deflazacort, as deflazacort is a more expensive, less available medication.

Discussion

The therapeutic effects of corticosteroids in preventing the progress of muscular dystrophy have been evaluated in many studies around the world. As no definite therapy has been found for this disease, corticosteroid treatment has been mentioned in textbooks of pediatric neurology for Duchenne dystrophy (4,5).

At the time being, two types of steroids have been suggested for this disease; namely, the common and routine type of prednisone and another type which is an oxazoline derivative of prednisone, called deflazacort. The main and basic question is "Which drug has better therapeutic effects?"

In this study, after one year of therapy, deflazacort was better than prednisone regarding motor function improvement ($p=0.001$), but at the end of the study (18 months after the beginning), there was no significant difference between these two medications in motor function improvement showing an equal effect of these drugs ($p=0.128$). This may be the result of excluding four patients from the prednisone group due to uncontrollable weight gain after the first year of the study. These were patients with severe reduction of motor function regardless of prednisone therapy. Those patients with a better situation in motor function under prednisone therapy stayed in the study causing the disappearance of statistical difference between the two groups after 18 months. If the patients were not excluded from the study, deflazacort would still be the permanent medication.

Regarding weight gain, one of the side effects of these medications, a significant difference between these two drugs after one year ($p=0.001$) and after completion of the study ($p=0.046$) was observed demonstrating that deflazacort causes less weight gain in contrast with prednisone.

About other side effects of these drugs, no decrease in height, increase in blood pressure, scoliosis, cataract, glucosuria, cardiomyopathy and motor function reduction was detected in the two groups; in explanation of this matter, we have to emphasize the low mean age of the patients regarding cardiomyopathy, scoliosis and reduction in motor function, which was 7 years; as in Duchenne muscular dystrophy, these complications are caused at higher ages. When the patients are bedridden, cardio-respiratory failure is the main cause of death and regarding height growth, diabetes, cataract and increase of blood pressure, more prolonged studies are necessary and mentioning a definite opinion about these complications is not possible.

In a study conducted by Marco D Banifati in Italy in 2000 (11), the impact of these medications was evaluated in a randomized double-blind study on a less number of patients in contrast with this study, in which 18 patients were enrolled in the study. The results showed the equal impact of the drugs on motor function and also the less influence of deflazacort on weight gain in contrast with prednisone. This indicates the same result as our study, apart the fact that we had a larger sample size pointing to a more valid statistical calculation.

In another study, carried out by Bernd Reitter in Germany in 1995 (12), the impact of these drugs were evaluated on 67 patients who had lost their movement ability. In physical examination, the muscle strength of twenty separate muscles was evaluated according to a 10 degree score 3 to 15 months after medication. These muscles were compared between the two groups. The dose of medications was exactly the same as our study. Finally, an equal influence was detected on the motor function between these two drugs. In addition deflazacort had less Impact on weight gain, similar to our study.

In another study, by WD Biggar in Italy and Canada in 2004 (5), two different deflazacort treatment protocols were assessed for Duchenne muscular dystrophy. One group used 0.6 mg/kg/day deflazacort for the 20 first days of the month and the other group used 0.9 mg/kg/day deflazacort everyday. Both groups had a separate control group using no medication. In this study, movement ability was better in the control group who was under no medication. The control group for the group under 0.9 mg/kg/day deflazacort everyday-which was the dose used in our study and most other studies, indicating the most efficient dose-had more significant motor ability. The interesting point in this study was the lower weight of patients under deflazacort therapy. Improvement in movement leading to physical activity; therefore, preventing weight gain in the treated patients was the reason for the lower weight. In our study, a similar result was detected; weight gain has direct influence on motor function reduction and if the patients using steroids control their weight based on nutritional advice, the influence of these medications, especially prednisone, on improvement of motor function is more significant. Maybe in our study, the Iranian diet with a higher fat content and also the higher parent affection in Iranians-paying more attention to the child-was the reason for weight gain in the deflazacort group.

In WD Biggar's study in 2000 (14), the impact of deflazacort was assessed on thirty 7 to 15-year-old Duchenne muscular dystrophy patients. The control group consisted of twenty-four patients under no therapy. In order to evaluate motor function, similar criteria to our study were used. The results emphasized the influence of deflazacort on maintenance of motor function in Duchenne muscular dystrophy. No glucosuria, blood pressure rise and uncontrollable infection were detected. Sylvie Houde et al's study in 2007 in Canada evaluating the impact of deflazacort on Duchenne muscular dystrophy (12) had a more prolonged follow-up than our study, which took eight years. This was a retrospective study on 79 patients. The treated group consisted of 37 patients and the non-treated group composed of 42 patients. The dose of medication prescribed was exactly similar to our study. In this study, the results showed the better influence of deflazacort in comparison to the group under no medication showing a two-year delay in getting bedridden in patients on deflazacort medication. Deflazacort is also efficient in the improvement of cardio-respiratory function consequently leading to development in the quality of life. Weight gain was a complication mentioned for this drug just like our study and the fact that this problem may be controlled by precise nutritional advice was also referred to.

In Biggar et al's study carried out in Canada and Italy (5), the excluded cases were those who worried about steroid consumption. This situation is pointed out by some physicians. In order to avoid such situations, the fact that the advantages of steroid prescription over the probable disadvantages in correct and indicated circumstances should be expressed in public health education. Deflazacort in comparison with prednisone is an expensive drug and this is the most important limitation in our study.

In conclusion, deflazacort is the best steroid for treatment of Duchenne muscular dystrophy with a better influence on the improvement of motor function compared with prednisone. In studies which demonstrate an equal effect of deflazacort and prednisone on motor function improvement, the former medication shows fewer side effects. On this account, as our study showed, if the patient's weight could be controlled when on prednisone medication, maybe prednisone could be prescribed instead of deflazacort when deflazacort prescription is not possible such as circumstances the patient can not afford to use deflazacort.

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Conflict of interest: not declared.

Ethical approval: In the 83rd Ethical Committee of Shahid Beheshti University of Medical Sciences, Number 88-01-146-6483-2852 Date: 89/12/2

The clinical trial code: IRCT201110047711N1

Table 1. The Mean Age of Patients in the Two Groups

	Prednisone	Deflazacort
Mean Age (year)	7.37±1.27	7.1±1.98

Table 2. Mean of Motor Function Index and Weight in the Two Groups

Variables	Group	Before Treatment	After 1 year	After 1.5 years
Mean ± SD (95% CI for mean) of Motor Function Index	P	5.0±0.53 (4.6-5.5)	5.25±1.03 (4.4-6.1)	5.75±1.67 (4.4-7.2)
	D	4.93±0.99 (4.4-5.5)	4.36±1.15 (3.7-5.0)	4.64±1.44 (3.8-5.5)
Mean ± SD (95% CI for mean) of Weight (Kg)	P	23.31±3.95 (20.0-26.6)	28.37±5.04 (24.2-32.6)	30.81±5.68 (26.1-35.6)
	D	20.39±4.63 (17.7-23.1)	23.03±5.51 (19.8-26.2)	24.71±5.67 (21.4-28.0)

Table 3. Mean of Change in the Motor Function Index and Weight and Comparison Between the Two Groups

Variables	Group	After 1 year	After 1.5 years
Mean ± SD (95% CI for mean) of Change of Motor Function Index (%)	P	↑5.20±18.07 (-9.9 – 20.3)	↑14.79±29.24 (-9.7 – 39.2)
	D	↓11.19±14.99 (-19.8 – -2.5)	↓4.52±26.46 (-19.8 – 10.7)
	Paired T- Test (P- value)	0.001	0.128
Mean ± SD (95% CI for mean) of Change of Weight (%)	P	↑21.65±6.68 (16.1 – 27.2)	↑32.04±8.88 (24.6 – 39.5)
	D	↑12.95±9.23 (7.6 – 18.3)	↑21.67±11.96 (14.8 – 28.6)
	Paired T-Test (P-value)	0.001	0.046

P value less than 0.05 as significant.

↑=increase, ↓=decrease

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