

# Retrospective cohort study comparing the efficacy of prednisolone and deflazacort in children with muscular dystrophy

## A 6 years' experience in a South Indian teaching hospital

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### ABSTRACT

**Background:** Muscular dystrophies are inherited myogenic disorders characterized by progressive muscle wasting and weakness of variable distribution and severity. They are a heterogeneous group characterized by variable degree of skeletal and cardiac muscle involvement. The most common and the most severe form of muscular dystrophy is DMD. Currently, there is no curative treatment for muscular dystrophies. Several drugs have been studied to retard the progression of the muscle weakness. There is much controversy about steroid usage in muscular dystrophy with respect to regimen, adverse effects, and whether long term benefits outweigh side effects. This study is to assess steroid efficacy in children with muscular dystrophy.

**Materials and Methods:** All children with diagnosed muscular dystrophy by muscle biopsy, immunohistochemistry and/or genetic test were enrolled in the study. They were started on either prednisolone (0.75 mg/kg/day) or deflazacort 0.9 mg/kg/day based on affordability. All were followed up every 6 months with clinical assessment, quality of life questionnaire and clinical and laboratory assessment of side effects. Outcome measures of children on deflazacort and prednisolone at 1 year followup were summarized as numbers and percentages and were compared using Fisher's exact test.

**Results:** Twenty two children with muscular dystrophy were included (prednisolone group: 10 and deflazacort group: 12). The mean age was 7.7 years at an average followup of 26.4 months. Twenty children were diagnosed to have Duchenne's; one had Becker's muscular dystrophy while one had sarcoglycanopathy by Type 2C. All children from prednisolone group maintained their ambulatory status at 2 and 4 years followups while three on deflazacort lost their ability to walk at an average age of 11.3 years. All activities of daily living were found to be better in prednisolone group. Muscle function and time taken to walk improved in prednisolone group. Weight gain in children on prednisolone was three times more.

**Conclusions:** Prednisolone is more beneficial than deflazacort at doses of 0.75 mg/kg/day and 0.9 mg/kg/day, respectively, however it is associated with adverse effects.

**Key words:** Becker, deflazacort, Duchenne, muscular dystrophy, prednisolone, steroids

**MeSH terms:** Steroid, muscular dystrophies, prednisolone, disabled children

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### INTRODUCTION

Muscular dystrophies are inherited myogenic disorders characterized by progressive muscle wasting and weakness of variable distribution and

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severity. They are a heterogeneous group characterized by variable degree of skeletal and cardiac muscle involvement.<sup>1,2</sup> They are divided into several groups based on the distribution of predominant muscle group weakness into Duchenne muscular dystrophy (DMD), Becker, Emery–Dreifuss, fascio-scapulo-humeral, limb-girdle, oculopharyngeal, and congenital muscular dystrophies.<sup>3,4</sup> The most common and the most severe form of muscular dystrophy is DMD. Genetic analysis is essential to establish an accurate diagnosis and for reliable genetic counseling and prenatal diagnosis.<sup>5</sup>

Currently, there is no curative treatment for muscular dystrophies. Several drugs have been studied to retard the progression of the muscle weakness. Corticosteroids have been reported in the literature to provide long term benefits. The mode of action of steroids is not well established, but is considered to be a combination of anabolic effect, immunosuppressant action reducing the number of cytotoxic lymphocytes, antifibrotic action and allowing muscle regeneration to proceed in a correct way, and also specific increase in some important membrane cell proteins such as utrophin, which is similar to dystrophin.<sup>6</sup> Steroids should be begun at the earliest possible in the course of disease.<sup>6</sup> Various randomized trials have shown to improve muscle function and strength in children treated with prednisolone.<sup>7–11</sup> Deflazacort has shown similar results but with lesser side effects.<sup>12,13</sup> Both deflazacort and prednisolone are equally effective in slowing the progression of disease when given at a dose of 0.9 mg/kg and 0.75 mg/kg, respectively, on daily basis, along with calcium and Vitamin D supplements.<sup>12</sup> Cochrane review suggests that even intermittent regimens are equally effective.<sup>14</sup> Merlini *et al.* concluded that early treatment prolongs ambulation by at least 3–4 years, based on a 10-year followup study of DMD patients who were started on prednisone at a mean age of 3.4 years.<sup>15</sup> Gorni *et al.* have shown that improvement is more evident in patients who are started on steroids at earlier ages.<sup>16</sup>

The efficacy and safety profile of one drug over the other is not well established. The purpose of our study was to evaluate our results of muscular dystrophy patients treated with two different steroids in a retrospective manner.

## MATERIALS AND METHODS

We retrospectively analyzed 36 children who received steroid therapy for muscular dystrophy between 2008 and 2013. Institutional Review Board clearance and patient consent were obtained. Three children who were started on steroids before the time frame of this study were also included as the same protocol was followed. Data were collected from

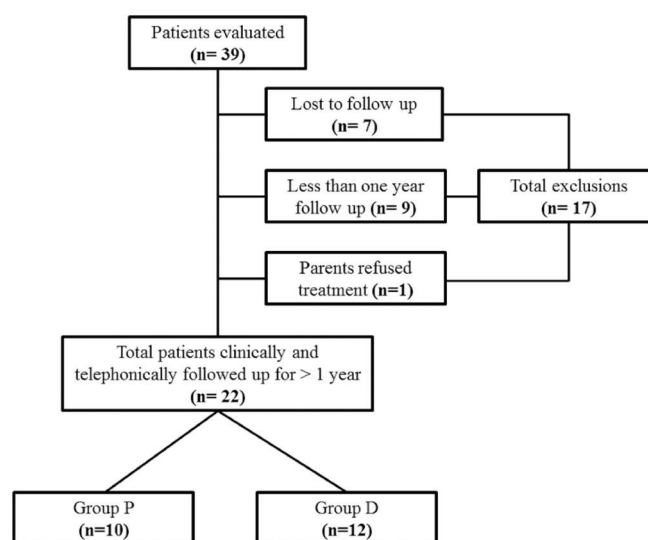
outpatient and in-patient records. Preoperative creatinine phosphokinase (CPK) levels were assessed to establish a preliminary diagnosis of muscular dystrophy. In the initial part of the study, diagnosis was established by immune-histopathology of biopsied muscle. The biopsy was taken from a partially involved muscle with more than grade 3 power. With the availability of genetic analysis for dystrophin gene in the latter part of study, this was used as the primary modality for diagnosis. When tested negative for abnormal gene, immuno-histopathology was considered.

Steroid therapy was initiated and supervised by a pediatric nephrologist. The parents were educated about the adverse effects of steroid usage. The preference of type of steroid, i.e. prednisolone or deflazacort was subjected to discretion of parents and based on their affordability. Children were divided into two cohorts; those receiving prednisolone (0.75 mg/kg/day) and those treated by deflazacort (0.9 mg/kg/day) [Figure 1].<sup>14,17</sup> Clinical parameters (blood pressure, weight, and height) and baseline investigations (blood glucose levels, serum creatinine, hemoglobin levels, DEXA scan, electrocardiogram, and spirometry) were assessed prior to initiation of steroid therapy. All were given calcium and vitamin D supplements. Lower limb deformities were addressed by serial corrective casting, stretching exercises or appropriate surgery, or orthosis following correction.

In all children, assessment and documentation of outcome measures were recorded on a pro forma.

Outcome measures:

- A. Maintenance of independent ambulatory status with or without orthotics



**Figure 1:** Flowchart showing exclusions and followup of enrolled children with muscular dystrophy

- B. Muscle functions: Assessed by timed tests (all measured in seconds)
- Time taken to get up from floor
  - Time taken to climb up four standard stairs
  - Time taken to walk 9 m
- These timed tests were assessed in the outpatient clinic with the help of a stop watch.
- C. Muscle strength assessment (Modified Medical Research Council [MRC] scale)

The following groups of muscles were assessed:

- Upper limb
    - Proximal muscles: Deltoid, biceps, and triceps
    - Distal muscles: Wrist flexors and extensors
  - Lower limb
    - Proximal muscles: Hip-iliopsoas, gluteus medius and maximus, knee-quadriceps, and hamstrings
    - Distal muscles: Ankle-tibialis anterior and posterior, tendoachilles
- D. Quality of life was subjectively assessed by questionnaires based on ability to perform activities of daily living, ability to write, play, and attend school. They were documented in Yes/No format.

Followup was done every 6 months after the initiation of treatment. Re-assessment of aforementioned clinical parameters, disease activity, and steroid side effects were done at every followup. These included assessment of levels of serum CPK, hemoglobin, fasting and postprandial glucose, DEXA scan, spirometry, and echocardiogram. Radiographs of spine and other regions were done, necessitated by symptoms and clinical assessment.

### Statistical methods

Types of muscular dystrophy were represented with numbers and percentages. Outcome measures of children at 1 year followup were summarized as numbers and percentages and were compared using Fisher's exact test. The median time taken to perform physical activities and average muscle powers were assessed at initial presentation and at 12 months. The change in time taken to perform physical activities from initial presentation to 12 months was also assessed using Wilcoxon signed-rank test in each group separately. The average weight gain between two groups was compared using two-sample *t*-test.

## RESULTS

Thirty six children were diagnosed with muscular dystrophy between January 2008 and May 2013. Three other children with DMD who were on same drug regimen

before commencement of the study were also included. Thus, 39 children with a mean age of 7.8 years (range 3–12 years) at the time of initial presentation were identified. There were 36 boys and three girls.

All the three girls had sarcoglycanopathy. Thirty one children were diagnosed to have DMD. Of the 39 children, 31 underwent muscle biopsy and 8 underwent only genetic analysis. Four patients underwent both muscle biopsy and genetic analysis. Two patients who had negative genetic analysis were proven to be positive by biopsy. The most common deletion found was that of exon 50 ( $n = 4$ ); others were in exons 47–52.

At presentation, lower limb deformities were common in these children. Ten had equinus deformities and three had knee flexion deformities. One patient had fixed elbow flexion and pronation deformity. None of the children had spinal deformity at initial visit. One child with DMD had a thoracic kyphosis of 45.9° at 2 years following therapy. However, initial radiographs were not taken and hence progression could not be documented.

Eighteen percent ( $n = 7$ ) of children were lost to clinical or telephonic followup after the initial evaluation. Sixteen children were clinically followed up and seven were followed up by telephonic questionnaires for more than 1 year. One child was not included in either group as parents refused treatment, but was on regular followup. The final cohort comprised these 22 children who were followed up for more than a year. Prednisolone group had 10 and deflazacort group had 12 children. All were boys with an average age of 7.7 years (range 3–12, standard deviation: 2.37) at the time of initiation of therapy. The average age in both groups were the same (prednisolone: 7.7 years, deflazacort: 7.8 years). Twenty children were diagnosed to have DMD, one had Becker's muscular dystrophy and one had limb girdle muscular dystrophy-2C. The average followup of 22 children was 26.4 months (range 12–60 months). The average duration of treatment was 26.6 months (range 4–60 months).

### Ambulatory status

At the time of initial evaluation, 20 children were able to walk independently and two (prednisolone group) were nonambulatory. All ambulant children from prednisolone group ( $n = 8$ ) maintained their ambulatory status at 1 year. One child on deflazacort lost ability to walk.

Eleven of the 13 children who were followed up for more than 2 years were ambulatory (prednisolone group:  $n = 5$ , deflazacort group:  $n = 8$ ). One child on

deflazacort lost ability to walk at 2-year followup and one on prednisolone who was a nonwalker at initiation of therapy maintained the same status.

While all children in the prednisolone group maintained ambulation at 1-, 2-, and 4-year followups, three of those on deflazacort lost their ability to walk at an average age of 11.3 years (range 9–15 years). Of the six patients who were followed up for more than 4 years (prednisolone group:  $n = 1$ , deflazacort group:  $n = 5$ ), one from deflazacort group lost ambulatory potential while the one on prednisolone continued ambulation.

Two children on prednisolone who were nonambulant at the beginning of therapy remained so at the end of 1 year. The mean age at loss of ambulation including those who were nonambulant at initial presentation was 10.9 years (range 9–15 years). Improvement in gait was noticed by the parents in eight children (47%). A 6-year-old boy with DMD who refused treatment but was advised physiotherapy came for followup 1 year lost his ambulatory potential and was bedridden at 7 years.

### Activities of daily living

At presentation, 13 children had difficulty and hence required assistance in attending toilet needs, whereas 10 were independent. After 1 year, only five out of these ten children were able to manage their toilet needs independently. Initially, 20 children were able to attend school with or without assistance. At 1 year, only 13 were school goers. Sixteen children were able to play outdoor or indoor games at the time of presentation, while only 10 were able to do so at 1-year followup.

The frequency of falls decreased in five children in deflazacort group (42%) and six in prednisolone group (60%). Parent satisfaction in both the groups was comparable; 42% and 50% in Groups D and P, respectively.

### Muscle function

Analysis has been done only for patients who were able to perform these tests at initial visit and last followup. The effect on these outcome measures has been summarized in Figure 2. The median time taken for performing activities was plotted. The change from baseline to 12 months was assessed using Wilcoxon signed-rank test. The changes were insignificant for all activities except walking. There was a significant improvement in time taken to walk 9 m in prednisolone group ( $P = 0.02$ ) whereas it has not shown any statistical significant improvement in deflazacort group.

### Muscle power

Total modified MRC grade is the average of upper and lower limb powers. Muscle power was considered deteriorated

when decreased by at least one MRC grade compared to initial power. All patients in both groups maintained same muscle powers at the end of 1 year of therapy. Five patients from prednisolone group and eight from deflazacort group who followed up at 2 years maintained same muscle power at the end of 2 years. All patients in both groups (prednisolone group:  $n = 1$ , deflazacort group:  $n = 5$ ) maintained same muscle power at 4-year followup.

### Creatinine phosphokinase

CPK levels were markedly elevated in all children. Values decreased in eight children (53.3%) and remained the same or increased in seven children. CPK levels were not available for eight patients at the time of final followup.

### Adverse effects

These values stress a significant risk of weight gain with the use of prednisolone using independent  $t$ -test ( $P = 0.01$ ). The average weight gain with both steroids was 3.45 kg per year. The mean weight gain was more in prednisolone group compared to deflazacort group ( $P = 0.02$ ). The power of statistical test for comparing weight gain between prednisolone group and deflazacort group using two-sample  $t$ -test was 71%. Cushingoid facies was significantly more in prednisolone group (prednisolone = 7 vs. deflazacort = 1) using Fisher's exact test ( $P = 0.02$ ). Significantly higher minor complications ( $P = 0.04$ ) were observed in prednisolone group (prednisolone = 60% vs. deflazacort = 16.7%) including gastritis, angular cheilitis, decreased growth velocity, and hypopigmented patches. An 11-year-old boy on prednisolone had decreased growth velocity (4 cm in 2 years). He was changed to alternate day regimen and cataract was ruled out. One patient on prednisolone therapy developed steroid toxicity which required tapering of steroid dose. None of the children had derangement of blood pressure.

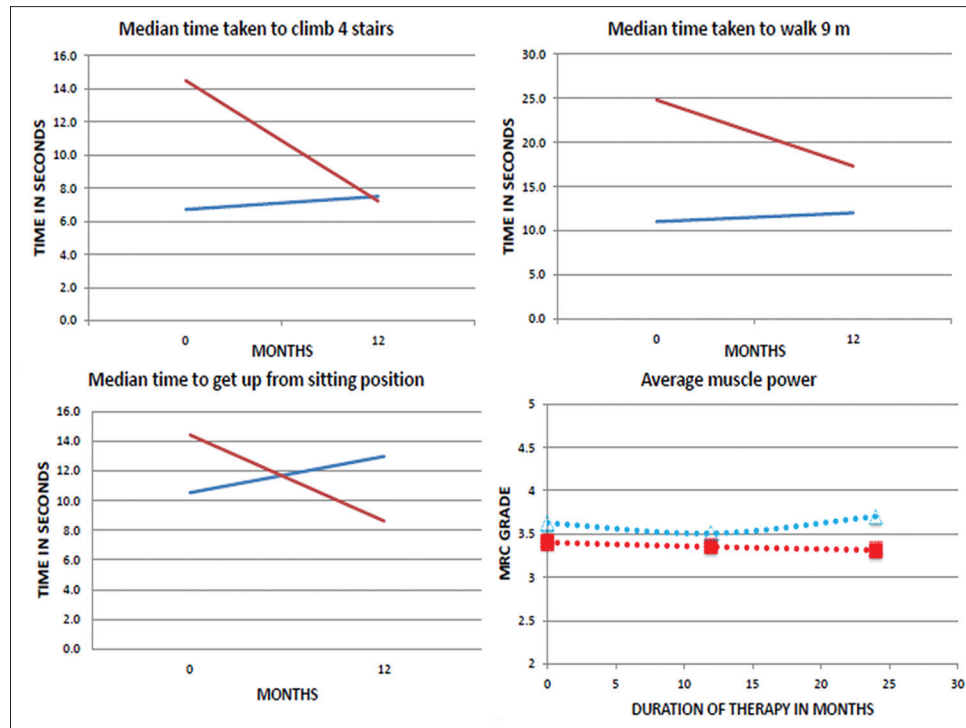
### Bone mineral density

BMD measured by DEXA was not uniformly monitored among all children. Hence, only descriptive analysis could be done. Among seven children, low values were documented for spine ( $< -1$  to  $-2.4$ ) in four and very low value ( $< -2.5$ ) in one child on deflazacort. However, none of the patients had symptoms related to osteoporosis such as bone pain and fractures.

### DISCUSSION

An ideal treatment of patients with muscular dystrophy would be to replace the defective gene product or replace the affected tissue, i.e., the myocyte with stem cell therapy. However, both are still in the stages of small animal experiments and have not been successful owing to large size of dystrophin and gene immune rejection.<sup>6,12</sup> Awaiting





**Figure 2:** Median time taken to perform various activities and average muscle power of extremities in deflazacort (blue trend line) and prednisolone (red trend line) groups

the positive results of stem cell or gene therapy, many forms of drug treatment have been tried to retard the muscle damage and improve the regeneration.

Steroids, mainly prednisolone and deflazacort, are the only drugs, which have been consistently proved to be effective, and also are the ones being studied for long term use.<sup>7-10,14-24</sup> Preliminary reports suggest that long term use helps prolong the ambulatory status, maintain the pulmonary function, and prevents or retards the progression of scoliosis. The results of the first cohort of these patients who will be going past their second decade are awaited.<sup>6</sup> However, there is still no consensus on preferred steroid, dosage, regimen, and duration, taking into consideration the functional improvement and side effects. The literature suggests the doses of prednisolone as 0.75 mg/kg and deflazacort as 0.9 mg/kg. According to Bonifati *et al.*, both are equally effective in slowing the progression of the disease.<sup>19</sup> The Cochrane review in contrast suggests that there is not enough data to compare the efficacy of these steroids.<sup>11</sup>

Knowing the natural course of the condition and lack of curative treatment, the aim of treatment with steroids is to delay the progression of muscle weakness and maintain physical activity irrespective of their ambulatory status. This is why children who were nonambulatory at the beginning of therapy were also included in the study. Lost muscle power will not be regained, but retardation of disease

progression is hypothesized and also preservation of cardiopulmonary function in the long run has been shown.<sup>23</sup> With the perspective of these muscular dystrophy patients, the fundamental requirement for a good quality of life is the ability to perform simple activities of daily living (walking, attending toilet needs, and going to school, writing, playing, and performing overhead activities) and hence these were considered for assessing the quality of life in our study. In a systematic Cochrane review of randomized and nonrandomized trials, improvement in strength and function was found to be similar with deflazacort and prednisolone. In contrast, our study showed improvement in the ability to perform day-to-day activities in the prednisolone group. Timed tests showed a statistically significant improvement in the prednisolone group, whereas a subtle increase in the duration of time in the deflazacort group. Activities of daily living and ambulation were maintained better in prednisolone group.

Glucocorticoids retard deterioration of muscle power when given over a short term.<sup>14,19</sup> Without treatment, most children with DMD lose their ability to walk by 9–11 years<sup>10,25</sup> or sometimes even earlier in case of severe phenotype. Muscle powers were maintained at same grades at all followups in both groups in our study.

Literature suggests that both deflazacort and prednisolone are equally effective in slowing the progression of disease when given at a dose of 0.9 mg/kg and 0.75 mg/kg,

respectively, on a daily basis.<sup>5,14,17,19,26</sup> Our study revealed a similar beneficial short term effect with steroids when given as a daily regimen.

Deterioration of ambulatory status can be expected, knowing the natural course of the disease. Twelve of the 13 children who came for followup at 2 years were ambulant. All children on prednisolone maintained their ambulatory status at 1-, 2- and 4-year followup.

Merlini *et al.* and Gorni *et al.* have shown that improvement is more evident in patients who are started on steroids at earlier ages.<sup>15,16</sup> The average age of initiation of therapy was the same in both groups (prednisolone group: 7.7 years and deflazacort group: 7.8 years). Five of the six children remained ambulant, when followed up for more than 4 years after the initiation of treatment. The average at the initiation of treatment in these children was 6.2 years. The longest followup in two children with DMD was 5 years after the initiation of treatment. One was on prednisolone and other was on deflazacort. Both maintained their ambulatory status at the latest followup of 11 and 9 years of age, respectively. A similar boy with DMD, who was 6-year-old when presented, lost his ambulatory potential as early as 7 years without treatment. These accentuate the fact that early initiation of steroids prolongs the ambulatory status and functional ability.

The disease course results in gradual loss of ambulation over time. The mean age at loss of ambulation including those who were nonambulant at initial presentation was 10.2 years (range 8–15 years). However, those who had not received prior treatment lost ambulation as early as 8.5 years. Those who were on steroids lost ambulation at 11.3 years on average (range 9–15 years). This again shows the beneficial role of steroids in improving the quality of life in children with muscular dystrophy.

Steroid therapy has a propensity to cause weight gain, with prednisolone having a higher risk<sup>14,17,24,25</sup> compared to deflazacort. In our study also, weight gain was the main side effect and those on prednisolone had almost three times more weight gain than those on deflazacort. Decrease in growth velocity has also been associated with long term use of steroids.<sup>14,27</sup> One child in our study with DMD had decreased growth velocity following prednisolone therapy. All other side effects such as cushingoid facies, gastritis, steroid toxicity, and hirsutism were more common with prednisolone. However, the beneficiary effect of prednisolone outweighs its side effects as most of the latter are easily manageable and reversible.

It appears as if the effect of prednisolone is better in comparison to deflazacort over a short term. However, this

being a small cohort with high rate of loss of followup, it is difficult to draw definite conclusions with regard to the efficacy of these two steroids in maintaining ambulatory potential and functional ability or with the incidence of adverse effects. Although there is no bias in selecting the steroid for treatment, we feel that another shortfall of this study is matching the children with different sub-phenotypes of DMD patients.<sup>28</sup> This could have been a confounding factor resulting in a better functional outcome in the prednisolone group.

A randomized controlled trial testing the efficacy of these drugs, matching sub-phenotypes, with a larger sample size and longer followup may have improved the quality of this study. These aspects may be given due consideration in further similar studies.

## CONCLUSIONS

Steroids have a definitive beneficial outcome on muscular dystrophies. Prednisolone and deflazacort at doses of 0.75 mg/kg/day and 0.9 mg/kg/day, respectively, are equally effective. Prednisolone is associated with significant weight gain, cushingoid features, and significant adverse effects. If not for cost constraints, deflazacort would be the preferred drug for the treatment of muscular dystrophies. Randomized long term, multi-centric trials are required to further substantiate the benefits and outcome.

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## Conflicts of interest

There are no conflicts of interest.

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