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Research Paper

Effective role of Beta 2 agonist in Duchenne's Muscular Dystrophy management – A review of 14 cases.

Medical Science

KEYWORDS :

Dr.Varun Singh	Residents , Deptt. Of Orthopaedics, NIMS Medical College and Hospital,Jaipur.
Dr.Mukesh Tiwari	Professor, Deptt. Of Orthopaedics, NIMS Medical College and Hospital,Jaipur.
Dr. Vikram Khanna	Residents , Deptt. Of Orthopaedics, NIMS Medical College and Hospital,Jaipur.

ABSTRACT

Duchenne's muscular dystrophy is one of the most common sex linked condition. This progressive muscular weakness is characterized by proximal muscle weakness and calf hypertrophy in boys. No treatment option is available for the same so the control of this disorder entirely depends upon genetic counselling. Here we present a case series of 14 cases of Duchenne's muscular dystrophy managed by various rehabilitative methods. The GSGC scoring system was used. The patients were divided into 3 groups in which group A was given physiotherapy, group B was given corticosteroids with Physiotherapy and group C was given all the above with beta 2 agonist. On comparing the results it was found that the superiority of the combined therapy is greater than the corticosteroids given alone.

Introduction:

Duchenne's muscular dystrophy is one of the most common sex linked condition with the prevalence of (1.7-4.2 per 100,000) [1]. It is characterized by progressive weakness. It is a progressive and lethal condition caused by the absence of dystrophin. Trials have been done to identify the gene responsible for this condition and the genetic genotypic expression for the adequate development of the dystrophin. This progressive muscular disorder is characterized by proximal muscle weakness and calf hypertrophy in boys. Patients usually become wheel chair bound and are unable to walk by the age of 12 years and generally perish due to cardiorespiratory complications by their late teens or early 20s[2].

No treatment option is available for the same so the control of this disorder entirely depends upon genetic counselling. As the males generally die before they can reproduce hence, the propagation of the disease entirely depends on carrier females which cause the transmission as an "X" linked recessive disease to the males. Also another way for the new cases to come into picture is by mutation of the X gene to cause the phenotype to appear [3].

Haldane's equilibrium theory for x-linked lethals states that in the absence of modifying processes one third of all affected males in a single generation should be sons of normal homozygous females [4]. In the last 4 years the focus has shifted to the better understanding of the proteins involved in the Duchenne's. Dystrophin the protein deficient in the Duchenne's muscular dystrophy has various pathophysiological consequences. It is a part of the DAPC (dystrophin-associated protein complex). The DAPC includes the dystroglycans, sarcoglycans, integrins and caveolin, and mutations in any of these components cause autosomally inherited muscular dystrophies [5]. The DAPC becomes destabilized if dystrophin is missing and this also causes the decrease in other proteins [6]. This inturn causes progressive membrane damage which causes the defective signaling [7]. The patients generally become wheelchair bound by the age of 12. Some patients also show the ECG changes by the age of 18 years.

In the present study patients of Duchenne's muscular dystrophy were managed by various rehabilitative methods and their outcomes compared to determine best possible intervention.

Material and Methods:

Here we present 14 cases of Duchenne's muscular dystrophy, treated with various treatment modalities between 2009 and 2014. After an informed consent a detailed history was taken and patients were examined clinically (Figure 1). Creatinine kinase estimation was done to find out the level of muscle destruction. Other test included electromyography, electrocardiography. After the above investigations patients were assessed using the GSGC (gait (G); climb a set of stairs (S); rise from a chair (C); rise from the floor (Gowers' maneuver) scoring system (table 1). After obtaining permission from ethical committee, patients were randomly distributed into 3 groups. In group one the patients were not given any pharmacological agent (group A), in the other group patients were given corticosteroids (group B) whereas in the third group patients were given beta-2 agonist along with the corticosteroids (group C).

In group A all patients were given detailed instructions regarding exercise, as without exercises there is more stiffness and further decrease in the functional status of the patients.

In group B apart from the physiotherapy and the exercises patients were prescribed 0.9 mg/kg body weight of Deflazacort for daily consumption.

Whereas, in group C patients were given Albuterol in the dose of 4 mg twice a day apart from the deflazacort and the exercises.

Patients were assessed using the following criteria:

- Change in the GSGC score
- Increase in the percentage of lean body mass
- Timed functional testing (time to walk 30 feet)

These patients were assessed initially to form a baseline for the same and then were assessed at 3 and 6 months to get the functional outcome of the various treatment modalities tried.

These results were then compared to find out if there was any advantage of giving any pharmacological agent. And if so then if there was any superiority of the result obtained by any one method or by giving both of them combined.

Results:

Out of 17 patients 3 were lost to follow up. All patients were males and of the age between 7-13 years (mean 9 years). The GSGC score was taken in the patients ranged from 14 - 19 (mean 17). Change in the GSGC score was measured in all three groups and it was noted that whereas the change in the score was marginal in group A, group B and group C showed remarkable decrease in the mean GSGC score indicating an improvement in the overall functional status of the patients (Figure 2). The result in group B and C were comparable with the final mean GSGC score in both the groups to be near 13.

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On assessing the increase in the lean body mass it was seen that there was marginal increase in group A whereas there was increase in group B and C (Figure 3). On comparing both group B and C it was seen that the percentage increase in the lean body mass in group B was 3.6% as compared to group C which was found to be 8.9% at the end of 6 months.

The time to walk 30 feet (Timed functional testing) was markedly reduced in group C as compared to the group A and B. In group C the time reduced by 5 seconds as compared to group A and B which showed the reduction by 1 and 3 seconds respectively.

General condition of the patients also improved in all the cases and all the patients benefitted from the various treatment modalities.

Discussion:

In cases of Duchenne's muscular dystrophy there is no definitive management. On a randomized control trial done in 1981 Clinical Investigation group of Duchenne Dystrophy (CIDD) was formed. In a study done to evaluate the various treatment options for the management of the Duchenne's muscular dystrophy. Out of a group of 14 drugs it was found that only steroids caused the stabilization of the power in DMD. In a study done by Mendell and CIDD group [8] it was found that the administration of prednisolone in children improved the power.

Prednisolone was compared with deflazacort and it was seen that deflazacort causes less weight gain and less loss of vertebral bone mass, which is very important in growing children and hence deflazacort has been used in DMD because of its potential 'bone-sparing' effect as compared to prednisolone but it is more likely to be associated with asymptomatic cataracts [9, 10].

The mechanism of action of steroids is not clear but various hypotheses have been proposed. One hypothesis states that the beneficial effect of Deflazacort on muscle has been associated with activation of the calcineurin/NF-AT pathway [11]. Another hypothesis states that the steroids reduce muscle necrosis and inflammation, although alternative actions may be modulating the cell response to inflammation [12]. Another cause for the beneficial effect may be due to the decrease in the muscle breakdown [13]. Another hypothesis may be that steroids may act as direct transcriptional modifiers to increase dystrophin expression in "reverted fibers", or increase synergistic molecules, such as muscle glycoproteins, that complement the action of dystrophin [14].

Hence, in our study deflazacort was used as there were less related complications as mentioned in the literature. Also it was seen that the duration of the treatment was short term that is 6 months to 2 years and in this short term of treatment it was seen that steroids significantly improve the muscle strength.

The treatment of DMD with a combination of Albuterol and corticosteroid the rationale of adding the albuterol was decided by the study done by Skura et al[15] in which it was concluded that short term increase in the muscle mass was noted but long term followup was needed to find out more about it. Previous studies have found a positive correlation between the lean body mass and the strength of the muscle [16, 17]. In our study it was seen that the lean body mass increased with the combination of corticosteroids and albuterol.

The mechanism of albuterol action is through binding to 2 receptors on the sarcolemmal membrane resulting in increased cytosolic cyclic AMP. While the exact mechanism of increase in the muscle mass is still not clear. It is thought that the mechanism is mainly by either increased muscle protein synthesis [18, 19] or decrease in the muscle protein breakdown [18, 20]. Suppression of the protein synthesis is thought to be the main mechanism of action. This suppression is thought out to be due to calpains which are calcium dependent proteas which causes the dystrophy to occur [21]. This can be prevented by the upregulation of calpastatin which easily done by Beta 2 agonist. The drug works better in a pulse therapy.

On searching the literature we managed to find a lot of encouraging results and hence we decided to give it in the group along with corticosteroids. And the results clearly highlight the superiority of the result as compared to getting corticosteroids alone, be it the lean body mass, strength or the GSGC score and hence, our results are in concordance with the results found in the literature.

Conclusion:

In our study it can be clearly seen that the superiority of the combined therapy is greater than the corticosteroids given alone. Although longer follow up and a larger sample size is necessary but a trial of combined therapy can be given for the management of Duchenne's muscular dystrophy.

Table 1. GSGC score.

Gait (G) 1. Normal 2. Mild waddling, lordosis and/or toe walking 3. Moderate waddling, lordosis and/or toe walking 4. Severe waddling, lordosis and/or toe walking 5. Walks only with assistance (i.e. braces, cane, crutches) 6. Stands, but unable to walk 7. Confined to wheelchair *Time to walk 10 meters: __ seconds*
Climbing stairs (S) 1. Climbs without assistance 2. Supports one hand on thigh 3. Supports both hands on thighs 4. Climb stairs in upright position but with aid of railing 5. Climbs while clinging to the railing with both hands 6. Manages to climb only a few steps 7. Unable to climb steps *Time to climb steps: __ seconds*
Gowers' maneuver (G) 1. Normal 2. Butt-first maneuver, one hand on floor 3. Butt-first maneuver, two hands on floor 4. Unilateral hand support on thigh 5. Bilateral hand support on thighs 6. Arises only with aid of an object (table, chair, etc.) 7. Unable to arise *Time to standing from sitting: __ seconds*
Arising from a chair (C) 1. Normal 2. With wide base and/or difficulty, but without support 3. With support on one thigh 4. With support on both thighs 5. With support on arms of chair or on a table 6. Not possible *Time to standing from sitting:_seconds*
Total GSGC Score: __ of 27

Figure 1: Showing Pseudo-hypertrophy of calf muscles in a patient affected with Duchenne Muscular Dystrophy.

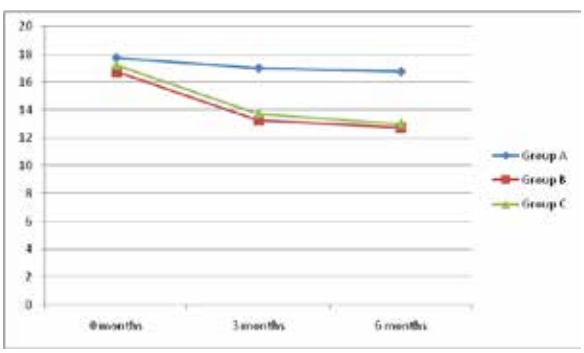

Figure 2: change in the mean GSGC score

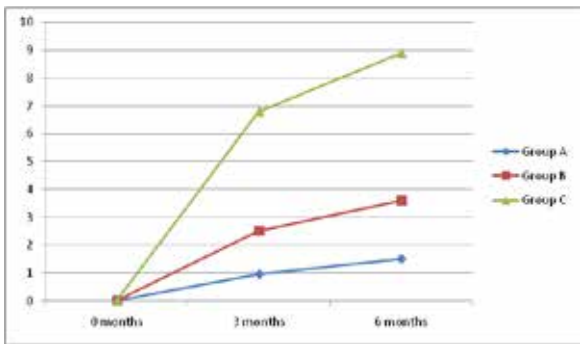

Figure 3: percentage change in the lean body mass

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