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The Effects of Enzyme Replacement Therapy in Patients with Mucopolysaccharidosis Type 1: A Case Series Study

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Abstract

Background: Mucopolysaccharidosis type I (MPS1) is caused by mutations in the gene which encodes the enzyme alpha-L-iduronidase. Deficiency of this enzyme causes a range of clinical symptoms in patients. The main treatment for MPS1 is hematopoietic stem cell transplantation. But its morbidity and mortality rates are significant and require matched marrow donors. Another method of treating MPS1 is enzyme replacement therapy (ERT). This study was performed to determine the effects of ERT in patients with MPS1.

Methods: Seven patients with MPS1, admitted in Imam Reza Hospital of Mashhad, Iran, during 2014, were included in the study. They were treated with a single dose (0.58 mg/kg) of enzyme laronidase and followed in 0, 3, 6, 9 and 12 months. The urinary glycosaminoglycan's (GAG), shoulder and elbow joint range of motion, volume of liver and spleen, and six-minute walking test were evaluated. Data was analyzed by SPSS software (version 16.0).

Results: The mean age of the patients was 22.43±5.85 months at the baseline. During follow-up, the level of urinary GAG showed a significant reduction ($p=0.004$), the volumes of liver ($p<0.001$) and spleen ($p=0.004$) were significantly reduced, and the result of 6-minute walking test was significantly increased ($p<0.001$). The side effects included generalized skin erythema as an allergic reaction in one patient and two episodes of fever during drug administration in one patient.

Conclusion: According to the results, the treatment with L-iduronidase in patients with MPS1 was effective and mostly safe.

Key Words: Enzyme replacement therapy, L-iduronidase, Mucopolysaccharidosis type 1.

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1- INTRODUCTION

Mucopolysaccharidosis is a progressive hereditary disorder. Inability to breakdown proteoglycans due to the absence or reduction of mutant lysosomal enzymes leads to accumulation of glycosaminoglycan parts in lysosomes. This accumulation of lysosomes inside the cell interferes with the cellular function and leads to the clinical, radiological and biochemical pattern of the disease (1). Mucopolysaccharidosis type 1 (MPS1) is caused by mutations in the gene which encodes the enzyme alpha-L-iduronidase. Deficiency of this enzyme causes a range of clinical symptoms from the severe (Hurler) to the mild (Scheie) disease (2, 3).

The main treatment for MPS1 is hematopoietic stem cell transplantation. However, this method has limited applications due to its considerable mortality and morbidity and needs Matched Marrow Donors. The other method of MPS1 treatment is ERT that is expected to reduce organomegaly, improve the joint growth and movements, reduce urinary GAG, and ultimately increase longevity and provide the patients with a better quality of life. FDA approved ERT through human alpha-L-iduronidase (Aldurazyme®) in 2003. It is administered at the dose of 100 U/Kg with 100 to 250 mL of normal saline (based on weight) (1).

In a study which investigated the first 5 years of treatment with L-iduronidase in patients with MPS1, the results demonstrated the high efficiency and significant impact of L-iduronidase on many systemic signs of progressive multi-organ disease (4). Another study used L-iduronidase enzyme for the treatment of patients with the mild form of MPS1. The results indicated that the use of L-iduronidase only reduces the volume of liver and spleen and the level of Glycosaminoglycans (5). Yet another study investigated the long-term effectiveness of L-iduronidase in the treatment of MPS1 during 3.5 years on 45 patients who had the milder form of the disease. The results indicated that early diagnosis and timely treatment led to more effectiveness of treatment with L-iduronidase in these patients (6). A research on the anthropometric data of MPS1 patients after treatment with L-iduronidase, reported a significant difference between the patients with MPS1 and the controls. The study showed that Children with MPS1 grew more slowly than ordinary individuals with respect to their age. The findings also show that the L-iduronidase does not cause changes in the growth of patients with MPS1 (7). A single-center cohort study proved the acceptable efficacy and safety of long-term ERT in children with MPS (8). Based on our knowledge, the present research is the first to evaluate the effectiveness and safety of ERT in Iranian MPS1 children.

2- MATERIALS AND METHODS

2-1. Study type and sample size

The study population included all patients with MPS1 referring to the pediatric endocrinology department in Imam Reza hospital, Mashhad, Iran, during 2014. In this case-series study, sampling was performed by a non-probability and easy method. Patient selection was confirmed by genetic and enzyme assay. According to the primary evaluation and previous research studies, the sample size included 10 cases. However, only 8 patients participated in the study and because of the death of one of the participants, the study's final population included 7 patients.

2-2. Inclusion and exclusion criteria

Iranians under 18 years of age who were newly diagnosed with MPS1 and had not been treated with enzymes were included in the study. Exclusion criteria were the patient's dissatisfaction to cooperate in the study, lack of regular weekly referring to

the hospital for treatment, and any comorbidity which distorts the study.

2-3. Treatment

ERT was performed from the beginning of the study. L-iduronidase or laronidase (Enzyme Aldurazyme, Genzyme Corporation) with a single dose of 0.58 mg/Kg (Vial 2.9 mg/5cc) was weekly injected.

2-4. Measurement and analysis

The urinary GAG levels were evaluated at different time intervals including 0, 3, 6, 9 and 12 months. The methodology was based on electrophoresis, which has been used to separate and determine the bands of dermatan, heparan and keratan sulfate in the urine to evaluate the response to treatment. The normal range based on the used kits was reported between 1.9 to 4.3 mg/mic mol (9). Also, at these times, the side effects of MPS1 (such as generalized skin erythema and fever) and the range of shoulder and elbow motion were assessed.

The range of motion was measured using a goniometer. The range of the patients' joints motion was measured during 4 movements including flexion, external rotation, abduction, and internal rotation while lying on their backs and sitting.

Moreover, at the baseline and follow-up times, abdominal ultrasound was performed to assess the volume of liver at midclavicular line and the volume of spleen. While the patient was lying on the back, an experienced radiologist performed the measurement using an ultrasound probe. The six-minute walk test was also done at the mentioned times. It was performed in a large space so that the child could walk in a straight line at his/her maximum speed without assistance from others; and the researcher measured the distance traveled by the patient in 6 minutes. Patients' height was measured by a Stadiometer at regular intervals of 3 months by a specific person at the endocrine clinic.

2-5. Ethical considerations

The research proposal of this study was approved by the ethics committee of Mashhad University of Medical Sciences (MUMS) with the code IR.MUMS.REC.1393.962 and also was confirmed by the Research Council of MUMS with the code 930988.

2-6. Data Analysis

The obtained data was analyzed by SPSS software (version 16). Data were reported using descriptive statistics. To compare the variables before and at different stages after the treatment, repeated measures (RM) test and Friedman test were applied for normally distributed data, and non-normally distributed data, respectively. $P<0.05$ was considered significant.

3- RESULTS

In this study, 7 patients including 4 males were evaluated. The mean age of the patients at the baseline was 22.43 ± 5.85 months (ranging from 8 to 30 months).

3-1. Urinary GAG levels

RM test showed significant changes on urinary GAG levels during the follow-up (**Table 1**). The LSD test revealed that the mean of urinary GAG levels at four follow-ups was significantly lower than that at the time of zero ($P<0.05$). **Fig. 1** shows the decreasing trend of urinary GAG levels at different stages of the follow-up.

3-2. Height and weight

According to the results of the RM test, the changes in the patients' height (**Table 2**) and weight (**Table 3**) during the follow-up were significant. The LSD test showed that the mean values of height and weight at the four follow-ups were significantly higher than those in the baseline ($P<0.05$). **Fig. 1** (B and C) shows an increasing trend in terms of height and weight in different

stages of the follow-up. **Table 4** demonstrates the Z-Scores of the patients before and after treatment.

Table-1: Mean and standard deviation of urinary GAG level of the patients during the follow-up

Urinary GAG level	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	190.71	87.13	49.6	27.01	11.8
SD	110.34	78.41	38.09	18.46	6.66
P-value of changes compared to the baseline measurements	-	0.001	0.003	0.004	0.004

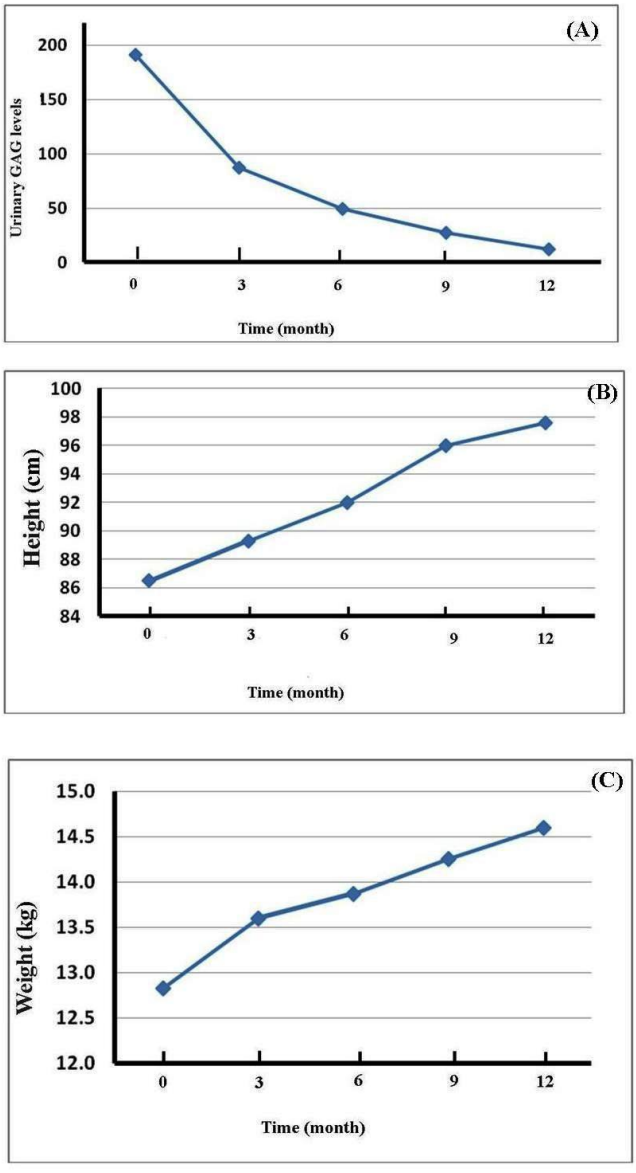

Fig. 1: Comparison of (A) urinary GAG levels, (B) patients' height and (C) weight during the follow-up periods (3, 6, 9, and 12 months)

Table-2: Mean and standard deviation of the patients' height during the follow-up

Height	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	86.5	89.29	92	96	97.57
SD	12.59	12.89	11.83	11.61	12.01
P-value of changes compared to the baseline measurements	-	0.030	0.001	0.001	0.001

Table-3: Mean and standard deviation of the patients' weight during the follow-up

weight	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	12.83	13.6	13.87	14.26	14.6
SD	3.34	3.5	3.45	3.64	3.69
P-value of changes compared to the baseline measurements	-	0.012	0.002	0.002	0.002

Table-4: Z-Score of the patients before and after the treatment

Patient's number	Z-Score before treatment	Z-Score after treatment
1	-2.20	-1.33
2	0.29	0.14
3	-1.50	-1.84
4	-1.26	-0.36
5	0.15	-0.35
6	-2.30	-2.55
7	-0.95	-1.18

3-3. The volume of liver and spleen

The percentage of liver and spleen volumes relative to the patients' height were assessed in different follow-ups and the RM test revealed significant differences, as compared to the baseline measurements. The LSD post hoc test showed that the mean values of spleen (**Table 5**) and liver (**Table 6**) volume at four follow-ups were significantly less than those of the baseline. **Fig. 2** (A and B) shows the decreasing trend in terms of spleen and liver volume in different follow-ups. The mean length of liver at the time of zero was 102 ± 12.68 mm and at the end of 12 months was 83 ± 12.88 mm. Similarly, the mean length of the spleen at the time of zero was 91.57 ± 12.07 mm and at the end of the 12 months was 81.7 ± 9.23 mm.

3-4. minute walking test

RM test showed significant changes in the result of the patients' 6-minute walking tests during the follow-up. The LSD post hoc test showed that the average score of the 6-minute walking tests at the four follow-ups was significantly higher than that at the time of zero (**Table 7**). Also, **Fig. 3** shows an increasing trend in terms of the scores of the 6-minute walking test in different follow-up stages.

Table-5: Mean and standard deviation of Spleen volume relative to the patients' height during the follow-up

Spleen volume relative to patients' height	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	10.75	9.91	9.35	8.57	8.35
SD	2.04	2.23	1.63	1.04	0.8
P-value of changes compared to the baseline measurement	-	0.019	0.001	0.002	0.003

Table-6: Mean and standard deviation of Liver volume relative to the patients' height during the follow-up

Liver volume relative to patients' height	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	11.87	10.69	9.93	8.88	8.53
SD	1.15	1.42	0.91	0.85	0.65
P-value of changes compared to the baseline measurement	-	0.028	P<0.001	0.001	P<0.001

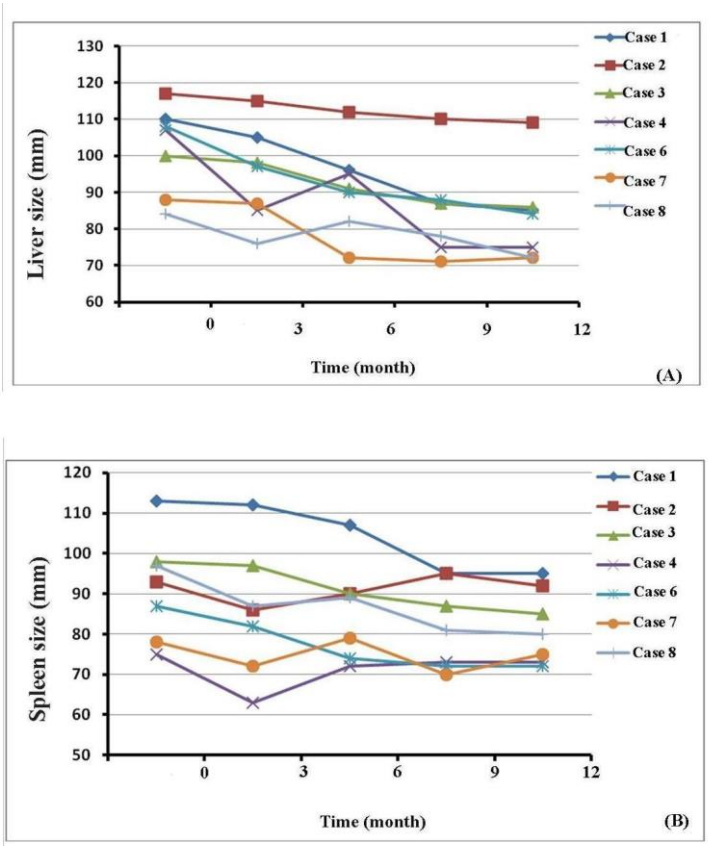

Fig. 2: Comparing the (A) liver and (B) spleen volume of the patients during the follow-up periods (3, 6, 9, and 12 months)

Table-7: Mean and standard deviation of the 6-minute walking test during the follow-up

6-minute walk test	Follow-up periods				
	Baseline	3 months later	6 months later	9 months later	12 months later
Mean	72	93.71	120	143	169.71
SD	75.48	71.79	84.85	78.9	87.32
P-value of changes compared to baseline	-	0.039	0.006	0.002	0.002

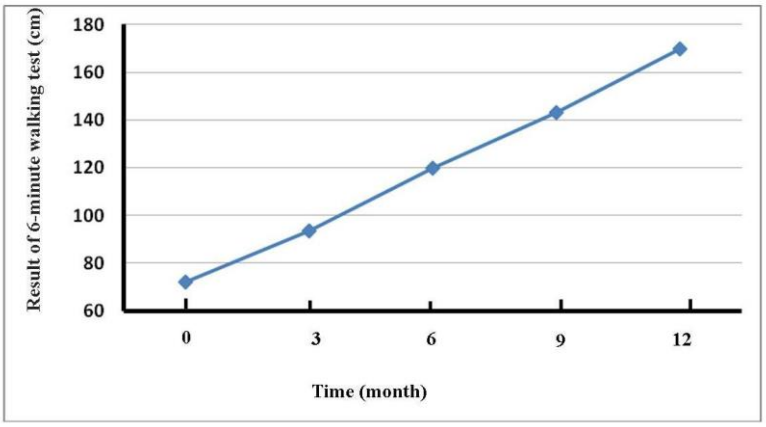

Fig. 3: Comparing the 6-minute walking test results during the follow-up periods (3, 6, 9, and 12 months)

3-5. The maximum movement range of the right and left shoulders and elbows in extension

Measuring the maximum movement of shoulder and elbow extension was done by a goniometer. The RM test showed a significant increase in the patients' maximum movement range of the right and left elbows and shoulders based on the degree of extension during the follow-up ($P<0.001$ for both the right and left shoulders, and $P<0.001$ for both elbows). The LSD test indicated that the mean values of maximum movement range of the right and left shoulders and elbows in extension at four follow-ups were significantly higher than those at the baseline ($P<0.05$). Also, the maximum movement range of the right and left shoulders and elbows in extension at different follow-ups showed an increasing trend for all of the patients. **Fig. 4** (A) shows the maximum range of movement of the right and left shoulders in extension during the follow-up period. **Fig. 5** demonstrates the maximum range of movement of the right and left elbow in extension during the follow-up period.

3-6. The maximum movement range of the right and left shoulder in flexion

The RM test showed significant changes in the patients' maximum movement range of the right and left elbows and shoulders based on the degree of flexion during the follow-up ($P<0.001$ for both shoulders and $P<0.001$ for both elbows). The LSD test indicated that the mean values of maximum movement range of right and left shoulders and elbows in flexion at four follow-ups were significantly higher than those at the baseline ($P<0.05$). Also, there was an increasing trend regarding the maximum movement range of the right and left shoulders and elbows in flexion at different follow-up stages for all patients. **Fig. 4** (B) shows the maximum range of movement of the right and left shoulders in flexion during the follow-up period.

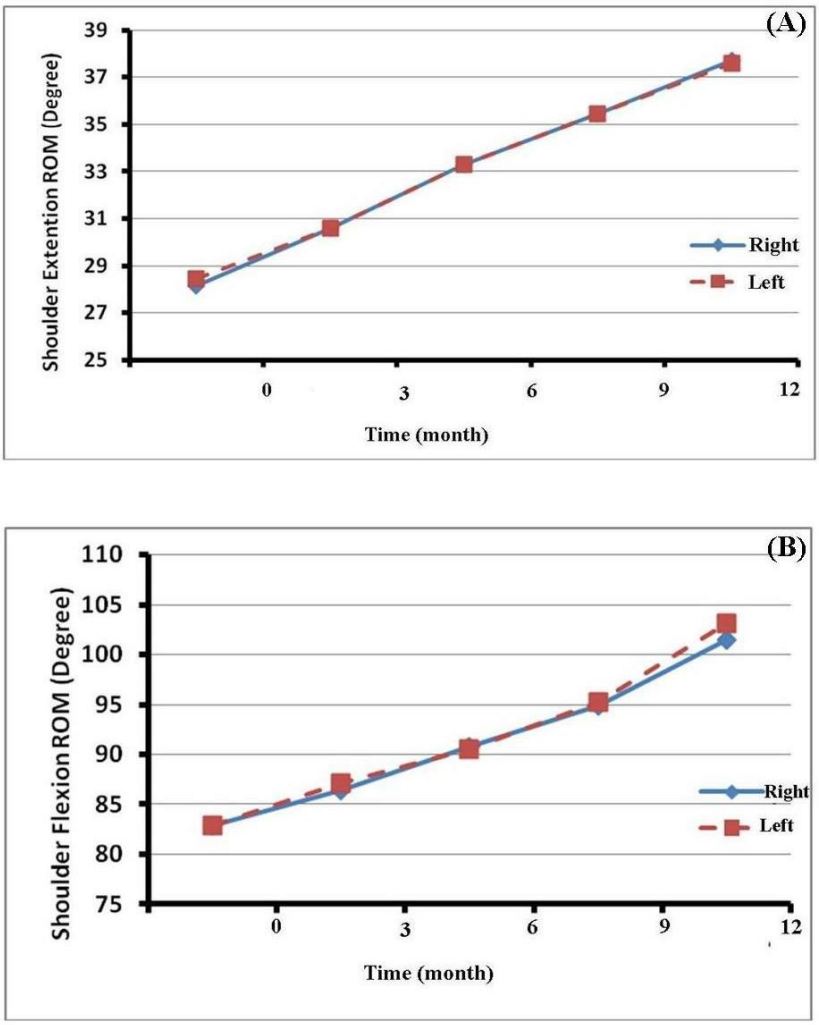

Fig. 4: Comparing the maximum range of movement (ROM) of the right and left shoulder in (A) extension and (B) in flexion during the follow-up periods (3, 6, 9, and 12 months)

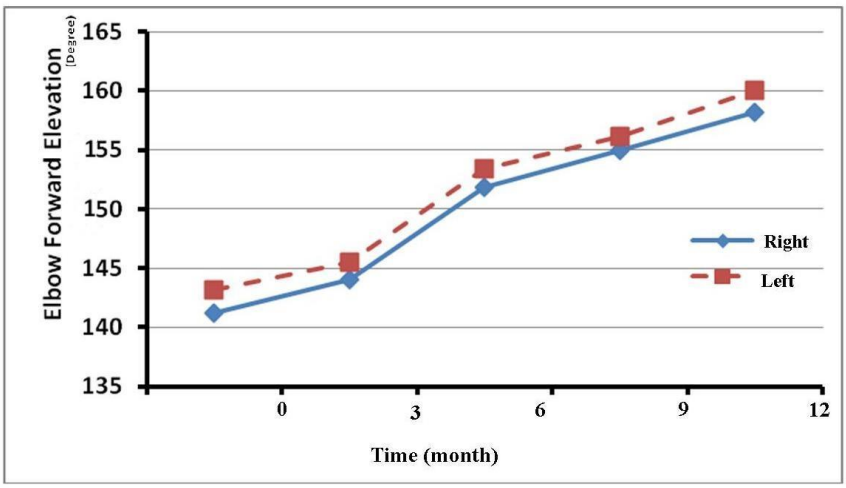

Fig. 5: Comparing the maximum movement range of the right and left elbows in different degrees of extension, during the follow-up stages (3, 6, 9, and 12 months)

3-7. Side effects

Evaluation of the side effects showed an allergic reaction as generalized skin erythema in one patient in the third month of the study. Moreover, fever was observed in the third and sixth months of the study because of the drug administration.

4- DISCUSSION

The findings of the present study indicated the appropriate efficacy of the treatment using L-iduronidase in patients with MPS1. According to the results, the changes of urinary GAG levels in the studied patients were significant during the follow-up and there was a decreasing trend in urinary GAG levels at different follow-up stages. Urinary GAG represents the amount of GAG, which is derived and discharged from the kidneys (10). In previous studies, it was found that the urinary GAG levels represent and reflect the accumulation of GAG in different organs (11). A review of the related literature showed the significant reduction of urinary GAG level after the treatment, similar to the findings of the present research (7, 12).

In this study, the mean values of patients' height and weight at the four follow-up stages from 3 months to 1 year were significantly higher than those at the baseline. Similarly, in a study on MPS1 patients treated with laronidase ERT, the mean value of the patients' height reached from 139 ± 19 to 159 ± 3 cm over 6 years of treatment. Furthermore, the mean weight of the patients reached from 40 ± 15 to 62 ± 10 kg during this period (12). Similar results regarding the patients' height and weight were found in other studies (4, 13). In a study in which the patients with MPS1 were divided into two groups, one group received enzyme therapy and the control group received placebo. Comparing the two groups in terms of height and weight changes revealed that the changes were not significant (P=0.84), suggesting the limited effects of the treatment on the bone and cartilage growth (7). Similarly, another study conducted on 8 patients with Hurler-Scheie syndrome showed no perceptible change in the height and weight of children after the treatment with L-iduronidase (5). Previous studies have suggested that perhaps the time to start the treatment with L-iduronidase is effective on the growth of height and weight, so that the later start of the treatment will decrease the possibility of normal height and weight in patients with MPS1 (7). Moreover, L-iduronidase in current treatment methods might not be able to reach growth plates (14). Some studies on MPS1 have shown that in this disease, fundamental changes are created in the structure of chondrocytes growth plates and perhaps this is the cause of no effects of L-iduronidase on height and weight growth of the patients (15, 16). However, it seems that more studies are needed to investigate the effect of this drug on the patients' weight and height.

The volume of liver and spleen was also measured in the present study. To eliminate the confounding variable of age and its effect on the volume of liver and spleen, the volume was measured as the percent of liver and spleen length on the patients' height in different follow-up stages. The volume of liver and spleen significantly reduced during the follow-up period. The standard volume of these two organs in the ultrasound of normal children was reported in the study of Konus et al. (17). By comparing the volume of these two organs between children in our study and that of the normal children, it was found that before the treatment the mean volume of the patients' liver was in the 95 percentile of height, while after the treatment the mean volume of liver was at the 50 percentile. Similarly, the mean volume of spleen before the treatment was in the 95 percentile of height and after the

treatment was in the 75 percentile. The findings are indicative of the good effect of the treatment with L-iduronidase on the volume of the patients' liver and spleen. In a study conducted on MPS1 patients treated with laronidase ERT for 6 years, the mean volume of liver and spleen reached normal volume in some patients (12). It seems that the studied treatment can be effective in improving hepatosplenomegaly in patients with MPS1 (6).

The mean score of the 6-minute walking test in all four follow-up stages was significantly higher than that at the time of zero. Since the patients at the baseline were old enough to be able to walk, it does not seem that age can improve the result of this test after the treatment. This finding indicates the good effects of L-iduronidase on improving bone and muscle strength and mobility in patients with MPS1. In a study by Clarke et al., the patients' 6-minute walk increased during the follow-up or at least remained unchanged (6). Our study also examined the maximum range of the elbow and shoulder motion before and after the treatment. It was observed that the maximum movement range of the right and left shoulders in both extension and flexion significantly increased during the follow-up period. In addition, the maximum change trend of the right and left elbow motion in extension significantly increased during the follow-up. These findings show the good effects of the treatment with L-iduronidase on the maximum range of the shoulder and elbow motion. These findings suggest that the motion range of these two joints was near to the normal range of motion during the follow-up. Since these two joints play an important role in daily functions and activities, the treatment with L-iduronidase could well enhance the quality of life in patients with MPS1. These findings have been also confirmed in other studies (6, 12).

With respect to the reported side effects, it can be said that L-iduronidase was well tolerated in patients with MPS1. The acute abdominal pain (12), skin changes and fever were side effects reported in other studies (6) and the last two complications are similar to those found in the present study; however, the side effects and the causes of them are not still well known.

In the study by Oda Silva Franco et al., although ERT was well tolerated and effective, it was not effective in preventing the progression of the disease or reducing the mortality rates. According to the findings of their study, early diagnosis and initiation of ERT were vital for improving the outcomes and quality of life (18). Based on a new review, while ERT and/or hematopoietic stem cell transplantation significantly improve the disease manifestations and lead to prolong life, the treatments can only partially prevent the disease (19).

A report regarding the clinical effectiveness and safety of long-term (2-8.3 years) ERT in Taiwanese patients with MPSI, demonstrated reduced levels of urinary GAGs and improved mobility, and joint function, as well as the liver and spleen volume. This study also showed that starting the treatment at a younger age will lead to better results (20). A systematic review and meta-analysis studying the efficacy of ERT in patients with MPS1 who initiated ERT in adulthood showed that ERT in adult age decreased GAG levels and liver volume and improved the 6-minute walk test (21). According to the results of another study by Concolino et al., the gold standard for the patients with severe types of MPSI such as Hurler is early hematopoietic stem cell transplantation. Scientific community believes that ERT must be applied in patients who do not have the possibility of receiving a more effective treatment. It has been widely suggested to screen neonates for the treatable MPS, because an early

treatment before the appearance of any symptom can affect the prognosis (22).

4-1. Study Limitations

Due to the limited number of samples available, it was not possible to conduct the study with the presence of a control group.

5- CONCLUSION

Since the urinary GAG levels significantly reduced in the patients, it can be concluded that the treatment with L-iduronidase had a good efficacy for patients with MPS1. Additionally, the volume of liver and spleen significantly reduced during the treatment and the range of joints' motion improved.

6- ACKNOWLEDGMENTS

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