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# Comparison of Daily versus Every Other Day Treatment Regimen of Levamisole to Control Recurrence in the Childhood Idiopathic Nephrotic Syndrome

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***Abstract***

***Background***

Idiopathic nephrotic syndrome is a kidney involvement that causes edema and heavy proteinuria with severe complications if the treatment is started late. The present study aimed to assess the efficacy of Levamisole in the daily versus every other day treatment regimen to control recurrence in Childhood Idiopathic Nephrotic Syndrome.

***Materials and Methods:*** This randomized clinical trial study was conducted on 52 children with Idiopathic Nephrotic Syndrome who referred to the pediatric nephrology clinic of Imam Reza Hospital of Kermanshah (Iran). The eligible patients divided into two groups using a random numbers table (Daily Group, n=10; Every Other Day Group, n=42). The first group received 2.5 mg /kg Levamisole daily and the second group received the same dose for every other day. Patients were investigated and followed up for at least 4 months. The clinical, laboratory variables, and side effects were compared between the two groups.

***Results:*** The two groups had no statistically significant difference in terms of baseline variables. There was a significant statistical difference between the two groups in terms of follow-up period after treatment using Levamisole, steroid dose, and the number of recurrences so that the average of these variables in every other day group was higher compared to the daily group ($P<0.05$). Also, there was no significant statistical difference between the two groups in terms of different complications of vomiting, arthritis, skin rash, neutropenia, seizure, increased liver enzymes, and Urea-Creatinine.

***Conclusion***

According to the results, the better efficacy and safety of Levamisole in the daily vs. every other day regimen, daily administration of Levamisole to control recurrence in the Childhood Idiopathic Nephrotic Syndrome was recommended.

***Key Words:*** Childhood, Idiopathic Nephrotic Syndrome, Iran, Levamisole.

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## 1- INTRODUCTION

Nephrotic Syndrome is a clinical condition that is caused due to glomerular damage. Indeed, this syndrome is a manifestation of glomerular disease, which is characterized by proteinuria in the nephrotic range(protein excretion > 40 mg/m2/h or > 50 mg/kg/day), triad of hypoalbuminemia (≤2.5 mg/dl), edema, hyperlipidemia (≥2.5 gr/dl), and protein/creatinine ratio of more than 2-3 at the first-morning urine sample symptoms (1-4). Nephrotic Syndrome, also known as nephrotic, is caused by damage to the Glomerular Basement Membrane (GBM) of the kidney and increased permeability in the Glomerular Filtration Barrier (GFB), and the kidneys excrete a large amount of protein (1, 2). Nephrotic Syndrome is characterized by symptoms of proteinuria in the nephrotic range (protein excretion > 40 mg/m2/h or > 50 mg/kg/day), triad of hypoalbuminemia (≤2.5 mg/dl), edema, hyperlipidemia (>2.6 mmol/L), and protein/creatinine ratio of more than 2-3 at the first-morning urine sample (3, 4).

Nephrotic Syndrome mainly occurs in children (in children 15 times more than adults) and is more common in boys compared to girls (2:1 ratio). Several studies have shown that the incidence rate of Childhood Nephrotic Syndrome is 2-7 per 10,0000 annually (5). Etiologically, Nephrotic Syndrome is divided into two types of primary and secondary. The major cause of primary Nephrotic Syndrome among children is an Idiopathic Nephrotic Syndrome (more 90%) and only about 10% of children with Nephrotic Syndrome have secondary Nephrotic Syndrome which is mainly caused by systemic or glomerular diseases (2, 6).

The purpose of Nephrotic Syndrome therapy is to reduce protein secretion in the urine, prevent infection, and reduce swelling. Corticosteroids were the first drugs that are used to the idiopathic nephrotic syndrome therapy. The main medicine of this group is Prednisolone. Many children with Nephrotic Syndrome experience a relapse at least once after the initial response. Recurrence also occurs in 50-60% of patients with discontinuation of treatment or reduced dose of Prednisolone (2, 7). Long-term use of Prednisolone may be effective in the treatment and reduce the relapses, but can lead to toxic effects of corticosteroids (2, 8, 9).

Immunosuppressive medicines are second-line medicines that are used as adjunctive therapy or corticosteroid replacement in the treatment of idiopathic Nephrotic Syndrome with reduced corticosteroid levels and their side effects. However, these medicines have potentially dangerous side effects (10-12). Levamisole, an anthelminthic medicine with immunomodulatory effects, was introduced as an adjunctive and corticosteroid dose-reducing medicine in the idiopathic Nephrotic Syndrome therapy. For the first time, Tanphaichitret al. introduced the beneficial effects of this medicine in Nephrotic Syndrome therapy (13). Then, various studies evaluated the effects of Levamisole in the treatment of this disease (11, 14, 15). However, studies with a control group are limited (11, 14, 15). On the other hand, in these studies, Levamisole 2.5mg/kg is used for every other day (11, 14, 15). Given that the limited number of Randomized Controlled Trials (RCTs) in Iran and the world, as well as a lack of studies on the daily consumption of Levamisole in the childhood Nephrotic Syndrome, this study aimed to compare the daily versus every other day treatment regimen of Levamisole to control recurrence in the childhood Idiopathic Nephrotic Syndrome.

## 2- MATERIALS AND METHODS

### 2-1. Study Design and Subjects

This study was a double-blinded Clinical Randomized Trial study (RCTs) that was conducted on 52 children

with Nephrotic Syndrome who referred to the pediatric nephrology clinic of Imam Reza Hospital of Kermanshah city (Iran). The sample size was estimated according to the previous related studies (11). Inclusion criteria involved informed consent of the patient's parents, age < 15 years, patients with steroid-dependent/frequently relapsed Idiopathic Nephrotic Syndrome and no use of other steroid-sparing agents. Exclusion criteria consisted of early recurrence (recurrence in the first month of treatment with every other day steroid), patients treated with Levamisole for less than 4 months, and lack of referral to complete treatment process and follow-up period.

### 2-2. Data Collection

In the present study, the data collection tool was a form designed by researchers, including the demographic variables (age and gender); clinical variables [duration of follow-up after treatment with Levamisole (month), steroid dose (mg/kg/month), time to first recurrence after the initial administration of Levamisole (month), and the number of recurrence], and side effects (vomiting, arthritis, skin rash, neutropenia, seizure, increased liver enzymes, and rising in Urea–Creatinine) which were measured for both groups.

### 2-3. Intervention

This study was a double-blind study. The sample population included all patients with idiopathic Nephrotic Syndrome who were not categorized in steroid-dependent or frequently relapsed patients that were referred to the pediatric nephrology clinic of Imam Reza Hospital Kermanshah city (Iran), and have not used other steroid-sparing agent, earlier (**Figure.1**). After obtaining informed consent from the patient's parents, the eligible patients were divided into two groups using a random numbers table (Daily Group, n=10; Every Other Day Group, n=42). Afterward, all patients in both groups were treated with Levamisole manufactured by ROUZ DARO Pharmaceutical Company of Iran. The first group received 2.5 mg /kg Levamisole daily (every morning) orally and the second group received the same dose for every other day. Afterward, patients in both groups were evaluated and followed up for at least 4 months. The dose and timing of Levamisole use were explained to the children's parents by a research colleague, and the medication was given to the children by the parents.

Patients were visited regularly every 1-2 months by a pediatric nephrologist. It should be noted that all these steps were the part of the patient's treatment and no cost was imposed on the patient. At each visit, patients were evaluated for laboratory and clinical factors including urea, creatinine, urine protein/Cr ratio, CBC, liver enzymes, recurrence rate, steroid dose, and side effects. All clinical and laboratory evaluations were performed at Imam Reza Hospital in Kermanshah city, Iran.

### 2-4. Ethical Considerations

Before the intervention, the goals of the study were fully explained to the patient's parents, then, if agreed, informed consent was obtained from them. In this study, all researchers were committed to the Helsinki Statement. This RCT study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (ID-number: IR.KUMS.REC.1398.687). Also, it was registered in the Iranian Registry of Clinical Trials (IRCT20180519039715N3).

### 2-5. Data Analysis

In the present study, mean (standard deviation), and frequency (%) were used for the descriptive analysis. Then, in inferential analysis, depending on the assumption of non-normality (according to Kolmogorov-Smirnov test), the Independent-Samples T-test and Mann–

Whitney U test was used for comparing the means of the quantitative variables between two groups under study. Also, for comparison of the qualitative variables in two groups, the Chi-square test, and Fisher's exact test were applied. It should be noted that the SPSS software version.16.0 was used for data analysis and P-value <0.05 was considered as a significant level.

## 3- RESULTS

This RCT study was conducted on 52 children with Nephrotic Syndrome. The patients were randomly divided into the two treatment groups of daily (n=10) and every other day (n=42). **Table.1** shows baseline characteristics among the two groups. The mean age of children in two groups of the daily and every other day was 6.001 ±3.48 and 6.41 ± 3.11 years, respectively. The number of boys and girls in the daily group was 6 (60%) vs. 4 (40%) and also for every other day were 24 (57.10%) vs. 18 (42.90%). Generally, there was no significant statistical difference between the two groups in terms of baseline variables of age and gender (P>0.05). The lack of significant statistical difference between the two groups in the term of baseline variables indicates that the randomization was carried out correctly.

**Table-1**: Comparison of Baseline Variables in Two Groups of Treatment Regimens of Daily and Every other Day.

| Variables | | Group | Number | Mean | SD | P-value |
|---|---|---|---|---|---|---|
| Age, year | | Daily | 10 | 6.001 | 3.48 | 0.685 |
| | | Every other Day | 42 | 6.41 | 3.11 | |
| Variables | | Daily | | Variables | | P-value |
| | | Number | % | Number | % | |
| **Sex of Patient | Male | 57.1 | 24 | 60 | 6 | 0.869 |
| | Female | 42.9 | 18 | 40 | 4 | |

*: Independent-Samples T-Test.
**: Chi-square Test, SD: Standard deviation.

**Table. 2** shows primary outcomes in two treatment regimens under study. According to the results of Mann–Whitney U and Independent-Samples t-tests, there is a significant statistical difference between the two groups in terms of duration of follow-up after treatment with Levamisole, steroid dose and the number of recurrences (P <0.05). So that the mean of these variables in every other day group was higher than in the daily group. However, no significant statistical difference was observed between the two groups in terms of time to the first recurrence after Levamisole initiation (P >0.05). **Table.3** presents side effects in two groups. According to the results of Mann–Whitney U and Independent-Samples t-test, there was no significant statistical difference between the two groups in terms of different complications of vomiting, arthritis, skin rash, neutropenia, seizure, increased liver enzymes, and rising Urea – Creatinine. So that the incidence of complications in the two groups was quite similar (P >0.05). Also, the results of the Chi-square test indicated that there was a significant statistical difference between the two in terms of recurrence, so that recurrence (%) in every other day group was higher than in the daily group (40 vs.73.80%)(P <0.05).

**Table-2**: Comparison of Primary Outcomes in Two Groups of Treatment Regimens of Daily and Every other Day.

| Variables | Group | Number | Mean | SD | P-value |
|---|---|---|---|---|---|
| * Duration of Follow-up after Levamisole Initiation (Month) | Daily | 10 | 14.40 | 10.24 | 0.001 |
| | Every other Day | 42 | 37.50 | 25.77 | |
| **Steroid Dose Levamisole Initiation (mg/kg/month) | Daily | 10 | 7.79 | 3.74 | 0.041 |
| | Every other Day | 42 | 11.33 | 5.00 | |
| *Time to First Recurrence after Levamisole Initiation (Month) | Daily | 10 | 10.74 | 14.38 | 0.516 |
| | Every other Day | 42 | 13.00 | 17.09 | |
| *The Number of Recurrences per month | Daily | 10 | 0.60 | 0.97 | 0.022 |
| | Every other Day | 42 | 1.64 | 1.39 | |

*: Mann–Whitney U Test.
**: Independent-Samples T-Test, SD: Standard deviation.

**Table-3**: Comparison of Side Effects in Two Groups of Treatment Regimens of Daily and Every other Day.

| Complications | | Daily Regime | | Every other Day Regime | | P-value |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| Recurrence | Yes | 4 | 40 | 31 | 73.80 | 0.041* |
| | No | 6 | 60 | 7 | 26.20 | |
| Vomiting | Yes | 0 | 0 | 0 | 0 | 1.00* |
| | No | 10 | 100 | 39 | 100 | |
| Skin Rash | Yes | 0 | 0 | 1 | 2.60 | 0.796* |
| | No | 10 | 100 | 38 | 97.40 | |
| Neutropenia | Yes | 0 | 0 | 0 | 0 | 1.00* |
| | No | 10 | 100 | 39 | 100 | |
| Seizure | Yes | 0 | 0 | 0 | 0 | 1.00* |
| | No | 10 | 100 | 39 | 100 | |
| Increased liver enzymes | Yes | 0 | 0 | 0 | 0 | 1.00* |
| | No | 10 | 100 | 39 | 100 | |
| Increased Urea - Creatinine | Yes | 0 | 0 | 0 | 0 | 1.00* |
| | No | 10 | 100 | 39 | 100 | |

* Chi-square Test.
**Fisher's exact Test.

## 4- DISCUSSION

The present study aimed to assess the efficacy of Levamisole in the daily versus every other day treatment regimen to control recurrence in childhood Idiopathic Nephrotic Syndrome. The results showed that there was a significant difference between the two groups of daily and every other day in terms of duration of follow-up after treatment with Levamisole, steroid dose, and the number of recurrences; so that the average of these variables in every other day group was higher than in daily group (P <0.05). Also, there were no significant difference between the two groups of daily and every other day in terms of different complications of vomiting, arthritis, skin rash, neutropenia, seizure, increased liver enzymes, and rising in Urea–Creatinine, so that the incidence of complications in the two groups were quite similar (P >0.05). The control group is one of the superiority of our study compared to previous studies (16-20). Gruppen et al. conducted an international multicenter study from six countries to determine the efficacy of Levamisole in increased recurrence time in children with steroid-sensitive Idiopathic

Nephrotic Syndrome. Consequently, the results showed a significant increase in the duration of recurrence after 12 months in the Levamisole group compared to the placebo. Also, after one year of treatment, 6% of the placebo group and 26% of Levamisole in the recovery period experienced no recurrence. They eventually concluded that Levamisole in children with steroid-sensitive Idiopathic Nephrotic Syndrome prolongs the recurrence-free period after therapy and also reduces the number of relapses in the first year of therapy compared to single corticosteroid therapy (19).

Sudha Ekambaram et al. aimed to assess the efficacy of Levamisole in frequently relapsing Nephrotic Syndrome and steroid-dependent Nephrotic Syndrome and demonstrated that Levamisole was effective in 77.3% of pediatric patients with a better efficacy (80.6%) in Frequently Relapsing Nephrotic Syndrome. Besides, this research showed a significant difference between means of steroid dose one-year before and one-year post-therapy by Levamisole (4109 ± 1154 vs. 661 ± 11 mg/m2; P <0.001). Also, less number of relapses was observed during the post-Levamisole therapy period (20).

Another study aimed to investigate the effect of Levamisole therapy in 72 children with Frequently Relapsing and steroid-dependent Nephrotic Syndrome (FRNS/SDNS) showed that the Levamisole caused relapse for 64.2% of the children at the treatment period and the first relapse occurred at 8.8 ± 8.1 months. There was a significant difference between the number of relapses before and after treatment using Levamisole (2.7 ±2.0 vs. 1.8 ±2.1 relapses/year, P = 0.02), and also a significant correlation between the two variables of time to first relapse and the total number of relapses (r = -0.56; P<0.001). Finally, the study argued that Levamisole is effective in reducing the number of relapses in children with Nephrotic Syndrome (21). A study to assess the effect of Levamisole on 304 children with Steroid-Dependent Nephrotic Syndrome in Iran, showed that after Levamisole administration, the means of steroid dose (0.39 ± 0.46 g to 0.33 ± 0.38 g), and the number of relapses (0.92 ± 0.98 to 1.07±1.20 per year; P< 0.001) were significantly reduced among the patients. Also, the administration of Levamisole for 14.5 months reduced corticosteroid dose and the number of relapses by 50% (22). Also, another study by Abeyagunawardena et al in Sri Lanka was aimed to evaluate the efficacy of daily consumption of (2.5 mg/kg) of Levamisole at 64 children with Nephrotic Syndrome previously treated with Levamisole and low-dose alternate-day prednisolone (a before-after study). Their results revealed that the mean number of relapses in patients on alternate-day Levamisole and daily Levamisoles were 2.81(±0.8), and 1.33 (±0.9); respectively, which this difference was statistically significant (P <0.001). However, there was no statistically significant difference between the two groups under study in terms of the side effects and liver enzyme levels (16). Given the above description, we concluded that the dialy consumption of Levamisole (2.5 mg/kg) can be effective and safe in the treatment of Childhood Idiopathic Nephrotic Syndrome.

### 4-1. Study Limitations

The present study had some strengths and limitations. According to our knowledge, this is the first interventional study that has investigated the efficacy of Levamisole in the daily versus every other day treatment regimen to control recurrence in the Childhood Idiopathic Nephrotic Syndrome. In other words, Levamisole was used in both comparison groups instead of the placebo. Also, this study, like many other studies, had some limitations. The most important limitation of this study was the unequal and low

number of patients in the two comparison groups and longer follow-up in every other day group, which led to reduced statistical efficiency of the study.

## 5- CONCLUSION

The results showed that the means of the follow-up period after treatment using the Levamisole, steroid dose, and the number of recurrences in every other day group were significantly higher compared to the daily group. Also, the incidence of complications including vomiting, arthritis, skin rash, neutropenia, seizure, increased liver enzymes, and rising in Urea–Creatinine in the two groups was quite similar. Therefore, the better efficacy and safety of Levamisole in the daily versus every other day regimen, daily administration of Levamisole to control recurrence in the Childhood Idiopathic Nephrotic Syndrome is recommended

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## 7- CONFLICT OF INTEREST: None.

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