ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

The Role of Azithromycin to Achieve Early Remission and Relapse Reduction in Children with Primary Nephrotic Syndrome — Randomized Controlled Trial

DOI: dx.doi.org

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Received: 21 November 2023
Accepted: 27 November 2023
Published: 28 November 2023

Published by:
Sheikh Sayera Khatun Medical College (SSKMC), Gopalganj, Bangladesh

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ABSTRACT

Introduction: *Nephrotic Syndrome (NS) is a common kidney disorder in children, marked by various complications. The standard treatment involves corticosteroids, but their prolonged use can lead to side effects. To address this, researchers have explored the potential of Azithromycin (AZM), an antibiotic with immune-modulating properties, as an adjunct to corticosteroid therapy.* ***Methods and materials:*** *This prospective randomized controlled trial was conducted at the Department of Paediatric Nephrology, National Institute of Kidney Diseases & Urology, Sher-E-Bangla Nagar, Dhaka, from November 2019 to June 2021. The study enrolled children aged 1-12 years with primary nephrotic syndrome (NS) during their initial episode and relapse, totaling 108 patients who provided informed*

(The Insight 2023; 6(1): 168-177)

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written consent from their parents. ***Results:*** *Initial attack NS patients, mean time to achieve remission was significantly lower in group A (7.74±2.78 days) who received azithromycin and prednisolone then group B (11.11±3.32 days) who received only prednisolone. (p<0.001). Similarly, among relapse case of NS, mean time required for remission was significantly lower in group C (7.63±2.54 days), who received prednisolone and azithromycin than group D (9.19±2.70 days), who received prednisolone only (p<0.034). In initial attack NS patients, number of relapse was lower in group A (20.0%) than group B (48.0%). [P<0.021] Similarly, among relapse patients, number of relapse was lower in group C patients (38.4%) than group D patient (48.0%).[p< 0.492]* ***Conclusion:*** *This study explored the impact of azithromycin treatment on initial and relapse cases in children with primary Nephrotic Syndrome (NS), and concluded that adding azithromycin along with prednisolone provided a greater benefit.*

Keywords: *Nephrotic Syndrome, Azithromycin Treatment, Children, Relapse Rates*

INTRODUCTION

Nephrotic Syndrome (NS) is a prevalent glomerular disorder affecting children, characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and generalized edema [1]. Its incidence varies globally, with higher rates observed in certain ethnic populations and geographical regions. While the majority of cases are primary (idiopathic), approximately 95%, the remainder are secondary to underlying causes [2]. Corticosteroids, particularly prednisolone, represent the cornerstone of treatment and often yield favorable responses [3]. However, managing NS can be challenging due to frequent relapses and the potential for adverse effects associated with prolonged corticosteroid use. The goal in treating pediatric NS is twofold: achieving remission as quickly as possible and minimizing the risk of relapse during and after corticosteroid therapy. Relapses necessitate extended corticosteroid treatment, which can lead to significant side effects such as growth retardation, obesity, hypertension, and osteoporosis, among others [4]. Therefore, pediatric nephrologists are continually seeking strategies to expedite remission and reduce relapse rates while mitigating the adverse effects of corticosteroids. Several steroid-sparing drugs, including levamisole, calcineurin inhibitors (such as tacrolimus and cyclosporine), cyclophosphamide, and mycophenolate mofetil (MMF)/mycophenolate sodium, have been employed to reduce the risk of relapse in children with steroid-resistant NS [5]. These medications have shown promise in maintaining remission and minimizing corticosteroid dependency. Azithromycin (AZM), a second-generation macrolide antibiotic, possesses anti-inflammatory and immunomodulatory properties. Beyond its antibacterial effects, AZM has been utilized in various pediatric conditions as an immune-modulating agent. Recent research suggests that a short course of AZM when administered concurrently with prednisolone during the induction of NS treatment, may enhance prednisolone sensitivity and hasten the achievement of remission [6]. Furthermore, AZM has demonstrated the potential to reduce the frequency of relapses in NS patients, possibly through its immune-modulatory effects, which may suppress inflammatory cytokines and reduce tumor necrosis factor (TNF-α) levels, known to

be elevated in nephrotic syndrome [6]. Additionally, AZM's antibacterial properties may correct underlying infections, further aiding in achieving early remission and reducing the number of relapses [7]. There is also evidence to suggest that AZM may impact renal epithelial cells, improving proteinuria by affecting the tight junctions of glomerular foot processes [8]. Given the potential benefits of AZM in terms of achieving early remission and reducing relapse rates, especially in children with primary nephrotic syndrome, it is crucial to rigorously evaluate its role as an adjuvant therapy to prednisolone. The aim of the study was to assess and compare relapse rates in children with primary nephrotic syndrome. By examining the efficacy and safety of AZM in this context, we seek to contribute to the development of more effective and less burdensome treatment strategies for pediatric NS, ultimately improving the quality of life for these young patients.

General objective:

- To see the efficacy of azithromycin in achieving remission early and maintenance of remission for a prolonged period in children with initial episodes and relapse cases of primary nephrotic syndrome.

Specific objective:

- To observe the time to achieve remission in both the intervention group (A, C) and control group (B, D).
- To observe the number of relapses in the intervention group (A, C) and control group (B, D).

METHODS & MATERIALS

This was a prospective randomized control trial conducted at the Department of Paediatric Nephrology at the National Institute of Kidney Diseases & Urology (NIKDU), Sher-E-Bangla Nagar, Dhaka, from November 2019 to June 2021. Children of age group 1-12 years with primary NS during initial episode and relapse were enrolled in this study and a total of 108 patients were included. Informed written consent was taken from the parents. Ethical clearance was obtained from the institutional ethical committee. On entry into the study, a detailed history was taken & proper physical examinations were done. Routine investigations such as complete blood count, CRP, serum albumin, serum cholesterol, serum creatinine, Mantoux test, screening tests for hepatitis-B & hepatitis-C, urine RME and culture sensitivity, X-ray chest, and serum C3 level were done. All investigation was done from NIKDU except the MT test that was done from Dhaka Shishu Hospital. Infection was screened out and appropriate measures were taken. Eligible patients were randomly categorized for initial attack NS into group -A (Intervention group) receiving prednisolone with azithromycin and group B (Control group) receiving prednisolone only. Where relapse case of NS was randomly categorized into group C (Intervention group) receiving prednisolone with azithromycin and group- D (Control group) receiving prednisolone only. During the initial episode of NS patients, Group A and B received prednisone 60 mg/m2/day (to a maximum of 60 mg/day) single morning dose for 6 weeks, followed by 40mg/m2/day (to a maximum of 40 mg/kg) on alternate days for 6 weeks.

Children with relapse cases of NS, Group C, and D received prednisolone 60mg/kg/day (maximum 60mg) up to remission for 3 consecutive days then 40mg/m2 (maximum 40mg) every alternate day for 4 weeks. Group A and Group C patients were treated with oral prednisone and azithromycin, whereas Group B and Group D patients were treated with oral prednisone only. Azithromycin was given orally in group A and group C at a dose of 10mg/kg/day for the first 5 consecutive days during induction of treatment with prednisolone after and followed by the first 5 consecutive days monthly for 5 months. Among relapse cases, patients, who received steroid-sparing agents were excluded from the study. During the treatment of NS patients in both intervention and control groups, if patients developed SRNS they were excluded from the study, and new patients were enrolled and randomly categorized into different groups like A, B, C, and D. All 4 groups (A, B, C, D) were followed up for 6 months at an interval of 3 months from the time of induction of treatment. During each follow-up visit children were observed to see the time to achieve remission, response to treatment, and relapses (if any). All the eligible patients enrolled in the hospital (indoor and outdoor). They were observed during hospital treatment, during discharge, and when at home (if needed). The data were collected and preserved in a case record form (CRF). The collected data were analyzed using Statistical Package for Social Sciences (SPSS) software, version 23.0. Independent student t-test and chi-square test were performed to compare the study variables where $p < 0.05$ considered as the level of significance with 95%CI.

Inclusion criteria:

- Children between 1 and 12 years old. (Pediatric age up to 18 years, but limited to 1-12 years due to facility constraints).
- Patients with primary (idiopathic) nephrotic syndrome.

Exclusion criteria:

- Children below 1 year and above 12 years of age with primary nephrotic syndrome.
- Children with secondary nephrotic syndrome (only primary nephrotic syndrome cases are included).
- Patients with Steroid-Resistant Nephrotic Syndrome (SRNS) are excluded.

RESULTS

Table I: Sociodemographic characteristics of 4 study groups (n=108)

Variables	Total (n=108)	Group A (n=27)	Group B (n=27)	Group C (n=27)	Group D (n=27)	*P* value
Age(years)	5.42±2.67	4.63±2.76	4.78±2.82	6.04±1.89	5.85±2.27	0.079†
Sex						
Male	73 (67.6%)	16	21(77.8%)	16	20	0.320*
Female	35 (32.4%)	11	6 (22.2%)	11	7 (25.9%)	
Residence						
Rural	77(71.29%)	21	18(66.7%)	18	20	0.748*
Urban	31 (28.7%)	6 (22.2%)	9 (33.3%)	9 (33.3%)	7 (25.9%)	

*P value measured by one-way ANOVA *P value measured by Chi-square (χ^2) test Age was expressed as Mean ± SD*

Among all the participants, the average age was 5.42 years, with Group D having the highest average age of 6.04 years. The p-value for differences in age among the groups was 0.079, indicating a lack of statistical significance. In terms of gender, 67.6% of the total participants were male, with Group B having the highest percentage of male participants at 77.8%. The p-value for gender differences among the groups was 0.320, suggesting no statistically significant difference. Regarding residence, 71.29% of the participants lived in rural areas, and no significant difference was observed among the groups (p-value = 0.748).

Table II: Time to achieve remission in an initial episode and at a relapse episode of primary NS (n=108).

Remission time (days)	Group A (n=27)	Group B (n=27)	*P* value	Group C (n=27)	Group D (n=27)	*P* value
<7 days	10 (37.0%)	2 (7.4%)	0.009*	8 (29.6%)	6 (22.2%)	0.535*
7-10 days	13 (48.1%)	12 (44.4%)	0.785*	14 (51.9%)	13 (48.1%)	0.785*
>10 days	4 (14.8%)	13 (48.1%)	0.008*	8 (29.6%)	8 (29.6%)	0.340*
Mean remission time (days)	7.74±2.78	11.11±3.32	<0.001†	7.63±2.54	9.19±2.70	0.034†

** P value measured by Chi-square (χ^2) test*

Table II shows the time to achieve remission in an initial episode and at a relapse episode of primary NS. Time required for remission was significantly shorter among intervention: group A (7.74±2.78 days) than control: group B (11.11±3.32 days) in the initial attack NS patients (p<0.001). Intervention: Group C's (7.63±2.54 days) required time for remission was also significantly shorter than control: group D's (9.19±2.70 days) in the relapse NS patients (p=0.034).

Table III: Number of relapses among group A and group B patients of the initial attack NS (n=50)

Relapse	Group A (n=25)	Group B (n=25)	*P* value
Yes	5 (20%)	12 (48%)	**0.037***
No	20 (80%)	13 (52%)	

Time of relapse (months)	5.75±0.87	4.20±1.64	**0.021†**

Out of 50 patients, 20% of Group A and 48% of Group B experienced relapses. The difference in the number of relapses between the two groups was statistically significant (p-value = 0.037). Additionally, the time of relapse was shorter for Group B (4.20 months) compared to Group A (5.75 months), with a statistically significant difference (p-value = 0.021).

Table IV: Number of relapses among group C and group D of relapse patients of NS (n=51)

Relapse	**Group C (n=26)**	**Group D (n=25)**	***P* value**
Yes	10 (38.46%)	12 (48%)	0.492*
No	16 (61.54%)	13 (52%)	
Time of relapse (months)	5.25±1.36	5.1±1.45	0.805†

Similarly, out of 51 patients, 38.46% of Group C and 48% of Group D had relapses. The difference in the number of relapses between the two groups was not statistically significant (p-value = 0.492). The time of relapse was similar for both groups, with no statistically significant difference observed (p-value = 0.805).

Table V: Number of relapses in group A and B patients at the 3rd month and 6th month of follow-up (n=17)

Follow	**Group**	**Group**	**P value***
At 3rd	1	1	0.496
At 6th	4	11	
Total	5	12	

Among the cases out of 17 patients, 20% of Group A and 8.33% of Group B experienced relapses in the 3rd month. In the 6th month, 80% of Group A and 91.66% of Group B had relapses. However, the difference in the number of relapses between the two groups at both time points was not statistically significant.

Table VI: Number of relapses in group C and D patients at the 3rd month and 6th month of follow-up (n=22)

Follow	**Group C**	**Group D**	**P**
At 3rd	3	3	0.793
At 6th	7	9	
Total	10	12	

Out of 22 patients, 30% of Group C and 25% of Group D experienced relapses in the 3rd month. In the 6th month, 70% of Group C and 75% of Group D had relapses. The difference in the number of relapses between the two groups at both time points was not statistically significant.

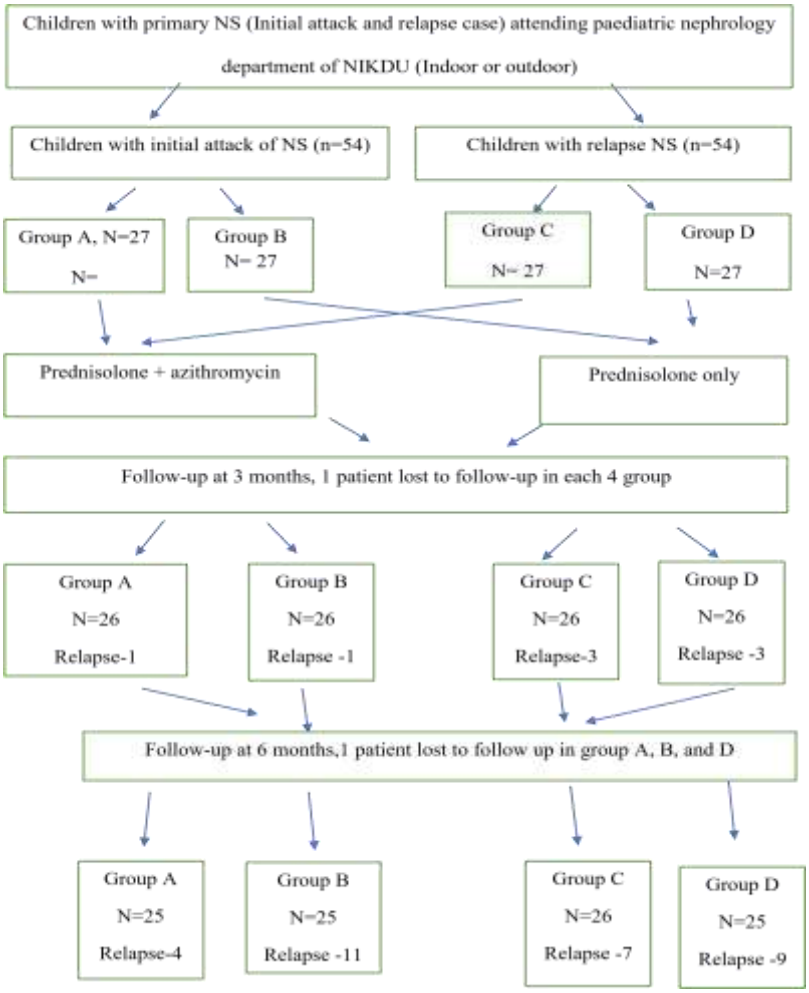

Figure 1: Flowchart showing treatment & relapse cases in different groups

DISCUSSION

In this study, the majority of children were male (67.6%). A study done by Esezobor, Solarin, and Gbadegesin showed similar sex distribution boys were 60.2% of the study population [9]. About 71.29% lived in rural areas. Among initial attack NS patients, the mean time to achieve remission was significantly lower in group A (7.74±2.78 days) who received azithromycin and prednisolone than in group B (11.11±3.32 days) who received only prednisolone (p<0.001). Similarly, among relapse cases of NS, the mean time required for remission was significantly lower in group C, who received prednisolone and azithromycin (7.63±2.54 days) than in group C, who received prednisolone only (9.19±2.70 days). Zhang and colleagues studied the effect of adding azithromycin to glucocorticoids in the treatment of primary nephrotic syndrome and found that the sensitivity of prednisone increased and concluded that adding azithromycin reduces duration to remission and decreases relapse in nephrotic children (Zhang et al. 2014) [10]. In this study, among initial attack NS patients, the number of relapses was lower in group A (20.0%) who received prednisolone and azithromycin than in group B (48.0%) those who were treated

with prednisolone only (p=0.021). Similarly, among relapse patients, the number of relapses was lower in group C patients (38.4%) who received prednisolone and azithromycin than in group D patients (48.0%) who received Prednisolone only (p=0.492). The mean time to start relapse was higher among intervention groups (group A and group C) compared to control groups (group B and group D). In the initial attack NS, at 3 months of follow-up, 1 patient in group A and B were lost to follow-up and 1 patient in both groups had relapse. But among relapse case patients, 1 patient was lost to follow up in both groups C and D and 3 have had relapse in both groups. In the initial attack NS, at 6 months follow up, 1 patient in groups A, and B were lost to follow- up and 4 patients showed relapse in group A, rather 10 patients had relapse in group B. In the relapse case of NS patients, at the 6^{th} month follow-up, 1 patient was lost to follow-up in group D 7 patients in group C and 9 patients in group D showed relapse again. In the study done by Zhang et al. 2014 the relapse rate was 11.6 % (11/95) in the intervention group (Azithromycin along with prednisolone), by contrast, the relapse rate was 21.4 % (21/98) in the control (prednisolone) group, and the relapse rate is significantly lower in the intervention group (p =0.049) at 3 months follow up. During 4 to 6 months of follow-up, the relapse rate in the intervention group (6/94, 6.25 %) was lower than that in the control group (11/96, 11.46 %), but the difference was insignificant (p =0.180) Azithromycin can help clear occult infections, such as sinusitis, chronic tonsillitis, dental caries, and acne, aside from its immunomodulatory and anti-inflammatory effects (Bagga et al. 2008) [11]. Azithromycin can improve proteinuria and maintain remission in several ways. Azithromycin may change the protein permeability of renal epithelial cells. In studies done on bronchial epithelial cells, Azithromycin increases the human airway transepithelial electrical resistance by affecting the processing of tight junction proteins (Asgrimsson et al. 2006) [12]. Recently, in a case report, azithromycin was reported to suppress relapses of idiopathic nephrotic syndrome in a 2-year-old boy. (Hara and Hirano 2018) [7]. There are immunomodulatory effects of azithromycin (Parnham et al. 2014) azithromycin down-regulates neutrophil chemokine production (IL-8, MPO) (Tamaoki, Kadota and Takizawa 2004) [13,14]. It attenuates T helper-1 cell responses following interferon-γ stimulation of macrophages, shifting activated macrophage polarization towards the alternative anti-inflammatory M_2-phenotype, which has a role in directing Th-2 responses and coordinating repair following inflammation (Yamauchi et al. 2009) [15]. It is capable of reducing TNF-α which may be partly, attributable to its ability to inhibit NF-kappa B (Cigana, Assael, and Melotti 2007) [16]. Khan and colleagues found that AZM was capable of reducing IL-1α and TNF-α in 100% of the studied individuals (Khan et al. 1999) [17]. In a study by Ikegaya and colleagues, they found that AZM inhibited about 40% of TNF-α release, in a human monocytic cell line. Also, they reported that Azithromycin reduced 34.6% of TNF-α production from lipopolysaccharide-stimulated healthy human monocytes (Ikegaya et al. 2009) [18]. Several studies have linked TNF-α activity and nephrotic syndrome in humans and animal models (Suranyi et al. 1993; Laflam and Garin 2006) [19,20]. Weissbach

and colleagues found a significant decline in TNF-α serum levels after corticosteroid treatment in children with steroid-sensitive but not steroid-resistant nephrotic syndrome (Weissbach et al. 2017) [21].

Limitation of the Study

The study included a relatively small sample size, which may not accurately represent the broader community.

CONCLUSION

This study explored the impact of azithromycin treatment on initial and relapse cases in children with primary Nephrotic Syndrome (NS), and concluded that adding azithromycin along with prednisolone provided a greater benefit, showing that, the time to achieve remission was shorter and number of relapses were fewer.

RECOMMENDATION

From this study, we found that azithromycin is effective in reducing the time to achieve remission and reducing number of relapses. So we can use azithromycin as adjuvant therapy with steroids in children with initial attack and relapse cases of primary (idiopathic) NS. Further multicentered extensive studies by including a large number of patients can be done to validate these findings.

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