ORIGINAL ARTICLE

A Pilot Study on the Effectiveness of Influenza Vaccination to Prevent Relapse of Steroid-Sensitive Nephrotic Syndrome in Children

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Abstract

Objectives
To study the effect of influenza vaccination in children with Steroid Sensitive Nephrotic Syndrome by comparing the frequency of viral Upper Respiratory Tract Infections (URI) and associated relapses from historic controls.

Materials and Methods
Trivalent, inactivated influenza vaccine (Influvac 2019/2020) was given to children with steroid-sensitive nephrotic syndrome before October 2019. They were either on low dose steroids or off medications and were observed for six months with recordings of their relapses and URIs. A comparison was drawn to the same number of unvaccinated children from the previous year.

Results
One hundred consecutive children were vaccinated. Five were lost to follow-up, so the effect on 95 children was compared with an equal number of unvaccinated children in 2018. The mean age of all the children was 4.7 ± 2.6 years (range 1-15 years) with a male to female ratio of 1.8:1. No immediate side effects or vaccine-related illnesses were seen in any patient. There were 17 episodes of URI in 16 (17%) children in the vaccinated group whereas 69 episodes in 59 (62%) children in the unvaccinated. Among the former, there were 55 episodes of relapses in 44 (46%) children while among the latter, there were 79 relapses in 71 (75%) patients. Both the number of URI episodes and relapses were significantly reduced in the vaccinated children ($p < 0.001$). The odds of getting URI and relapse in them were 0.12 (95% CI 0.06-0.24) and 0.29 (95% CI 0.16-0.54) respectively. No difference was seen in the number of relapses that were not associated with URI.

Conclusion
There seems to be a significant decrease in all-cause URI and relapses in steroid-sensitive nephrotic children who are vaccinated with influenza vaccine. Further trials in larger cohorts are required to confirm the safety and beneficial effect of the recommended vaccination.

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Keywords
Steroid-sensitive Nephrotic Syndrome, Viral Upper Respiratory Tract Infections, Influenza Vaccine.

Introduction

It is a well-established fact that upper respiratory tract infection (URI) usually trigger relapses in steroid-sensitive nephrotic syndrome (SSNS).[1,2] Several implicated factors include the loss of immunoglobulin, properdin, and complement in the urine.[2] Various studies have documented the prevalence of infections in nephrotic syndrome (NS worldwide). Moorani et al in two different studies have documented 29% and 54% URIs in nephrotic children of Pakistan.[3,4] The use of preventive strategies such as immunoglobulin (IVIG), Chinese herbal medications, polyvalent bacterial vaccines, zinc supplementation, and BCG vaccine have shown variable results.[4,5] Low-dose steroids, when used for 5-7 days, reduce the frequency of relapses triggered by URI.[6,7] Once a child with SSNS develops URI, they receive a recommended low dose of steroids as the standard of care. Some of them improve, while others may have persistent proteinuria and get treatment for relapse.

The influenza vaccine, when given to children with recurrent acute otitis media (rAOM) by any infectious agent, reduced the incidence of new episodes of rAOM and antibiotic use.[8] Some regional guidelines do recommend yearly influenza vaccines for nephrotic children owing to their immunosuppressed status.[9] We hypothesized that the influenza vaccine may prevent URI from not only the influenza virus but other viruses also. There is insufficient data about the rate of relapse in nephrotic children who develop URI after receiving the recommended low-dose steroids for 6 days and being vaccinated.

We wanted to compare the response to low-dose steroids for one week among the vaccinated children, as compared to the non-vaccinated. Since it would be unfair not to offer vaccination to the control group, we used historic controls from the previous year of unvaccinated children. This pilot study would help to establish the beneficial effects of the influenza vaccination in this select group of patients and pave the way for future longitudinal studies.

Material and Methods

We conducted an experimental study at the Pediatric Nephrology department at the Sindh Institute of Urology and Transplantation,

Karachi, Pakistan. Through consecutive non-probability sampling, children up to the age of 18 years with SSNS received 0.5 ml of trivalent inactivated Influenza Vaccine (Influvac 2019/2020). These children were either in remission or were taking low-dose steroids on alternate days. All the children were observed for immediate side effects of vaccination for up to an hour and then after one week. The number of URI episodes and relapses after vaccination over a 6-month period were recorded. We then compared the outcome of similar patients who had not received the vaccine in the year 2018. Children with congenital nephrotic syndrome, infantile nephrotic syndrome, primary and secondary steroid-resistant nephrotic syndrome, nephrotic syndrome secondary to systemic diseases, and children using second-line drugs like levamisole, cyclophosphamide, and cyclosporine were excluded.

After approval from the institutional Ethics Review Committee (ERC), we obtained informed consent for vaccination and participation in research from the parents or guardians of all the children and assent from all the adolescent patients. We used a pre-designed questionnaire for all the data and maintained the confidentiality of all the participants. Nephrotic syndrome was defined as edema, urine protein creatinine ratio >2g/g or urine dipstick +3 protein and hypoalbuminemia< 2.5 g/dl. Remission was characterized as urine protein creatinine ratio of < 0.2g/g or < 1+ protein on dipstick for 3 consecutive days.[9] Relapse was considered to be urine protein creatinine ratio of >2g/g or urine dipstick +3 for 3 consecutive days after having been in remission.[9]

Upper Respiratory Tract Infection (URI) was defined by the presence of at least two of the three following symptoms: runny nose, cough, and fever (for at least 24 hours).[10]

Statistical Analysis

The demographic and anthropometric characteristics were compared using an independent T-test for continuous variables and a Chi-square test for categorical variables using SPSS software version 22. A p-value of <0.05 was considered significant.

Results

One hundred consecutive children with SSNS received the flu vaccine in October 2019 before the start of flu season. Five children were lost to follow-up, so the final analysis was done for 95 cases over a period of 6 months. To compare the effect of vaccination on the frequency of URI and related relapses, the same number of children with SSNS who presented with URI in 2018 were taken as historic controls.

None of the patients had any immediate side effects like allergic reaction, acute flu-like symptoms, and injection-related complications to the vaccination within one week in our cohort.

The demographic details of both the cases and controls are illustrated in Table 1. The mean age of children in cases and controls were 5.2 years ± 2.7(1-15years) and 4.2 years ± 2.5 (1-12 years) respectively. In both groups, the male to female ratio was 1.8:1.

Table 2 demonstrates the total number of URI episodes and relapses in both vaccinated and unvaccinated children. Of the children who were vaccinated, there were total 55 episodes of relapses in 44 (46%) children. Out of these, 16 (17%) had a URI episode and 11 (12%) patients had 12 episodes of URI-related relapse while the remaining 5 (5%) recovered from URI with low dose steroids for a week. In comparison, the unvaccinated children had a total of 79 episodes of relapses in 71 (75%) children. Out of these 65 (68%), children had URI

Table 1: Demographic details of vaccinated and unvaccinated children

	Vaccinated Children n = 95	Non-vaccinated Children n = 95	p value
Mean Age ± SD years	5.2 ± 2.7	4.2 ± 2.5	
Male n (%)	34 (35%)	33 (35%)	0.02
Female n (%)	61 (65%)	62 (65%)	
Male: Female ratio	1.8:1	1.8:1	

Table 2: Upper Respiratory Infection (URI) and relapses in vaccinated versus unvaccinated children

	Vaccinated Children n =95	Non-vaccinated Children n = 95	p value
Total Patients with Relapse	44 (46%)	71 (75%)	<0.01
Total Relapse episodes	55	79	<0.01
Total patients with URI	16 (17%)	65 (68%)	<0.01
Recovered (%)	5 (31%)	22 (23%)	<0.01
URI related Relapse	11 (12%) patients with 12 episodes	43 (45%) patients with 43 episodes	<0.01
Relapse without URI	33 (35%) patients with 43 episodes	28 (29%) patients with 36 episodes	0.18

and 43 (45%) patients had 43 episodes of URI-related relapse while the remaining 22 (23%) patients recovered from URI with low dose steroids. In both vaccinated and unvaccinated groups, there were 43 and 36 episodes of relapses respectively which were not preceded by any viral infection. The difference in the number of URI episodes and relapses between vaccinated and unvaccinated children is also shown graphically in Figure 1.

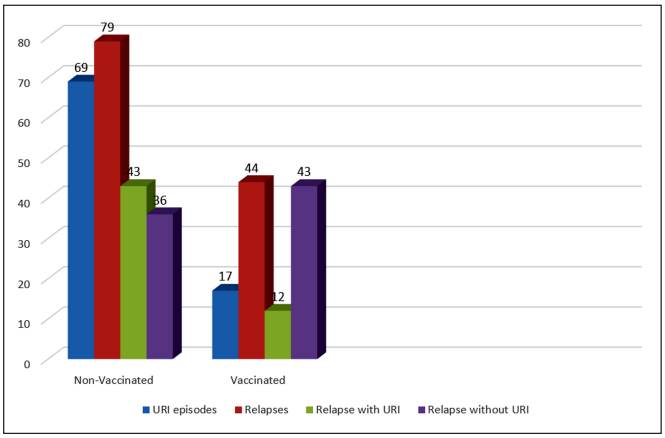

Fig 1. Difference in URI and Relapse episodes in vaccinated versus non-vaccinated children in percentages.

When the two groups were compared, there was a statistically significantly lower number of URI episodes, 16 (17%) vs 65 (68%) (p-value <0.001), and URI-related relapses of 12 vs 43 (p-value <0.001), in the vaccinated children. The odds of getting a URI episode with or without relapse for a vaccinated child were 0.12 (95% CI 0.06-0.24) while the odds of having a relapse in a vaccinated child associated with URI was 0.29 (95% CI 0.16-0.54)

Discussion

This pilot project has shown a significant role of influenza vaccination in the prevention of all-cause URI and relapses in children with Steroid Sensitive Nephrotic Syndrome. There is very little known about the incidence of Influenza infections in children of Pakistan. Globally, it can contribute to up to 13% of all pneumonia and 7% of severe diseases in children less than 5 years of age.[10] The risk of acquiring serious secondary infections after a viral URI are higher, therefore, it is recommended that this vaccine should be given annually to all people at a higher risk.[11] CDC recommends annual vaccinations for all above 6 months of age.[12] The KDIGO clinical practice guidelines for glomerulonephritis 2012 and the 2021 revised guidelines for SSNS from India also recommend annual influenza vaccination in children with SSNS to reduce the incidence and severity of influenza infection.[7, 9]

The role of influenza vaccination in preventing influenza infections is well established for a long time; however, to the best of our knowledge, this is the first study that has looked into its role in this specific group of children. Marchisio *et al* reported an interesting finding in a randomized trial of 180 children who were less than 5 years of age and had recurrent episodes of acute otitis media (AOM). They found that by vaccinating children against influenza, not only the number of episodes of AOM from any etiology was reduced, but also the severity was less among vaccinated children. We have also found that children who were vaccinated against influenza had fewer episodes of URI as compared to unvaccinated children in the previous year. Moreover, vaccinated children were less likely to develop a relapse of NS after a preceding URI as compared to unvaccinated children.

The exact reason for this finding is unknown. About 200 viruses can cause URI. Some of the commonly implicated viruses are rhinovirus, parainfluenza virus, adenovirus, coronavirus, coxsackievirus, echovirus, and respiratory syncytial virus (RSV).[13,14] The flu vaccine is known to increase the antibody titers manifold against influenza over the course of 6 months.[15] We may hypothesize from our results that these higher antibody titers may have a protective role against other viruses too.

It was observed that in the vaccinated children the number of relapses that were not associated with a URI was similar in comparison to non-vaccinated children. It may be interpreted that the protective effect on relapses in vaccinated children is only seen in relapses associated with a viral URI, and not otherwise.

No side effects were seen and that establishes the safety of this vaccine in this group of children; however, the sample size was not large enough to generalize this finding.

It is also worthwhile to mention in this discussion that not every vaccine is as effective and safe in nephrotic children. Abeyagunawardena *et al*. showed an increased risk of NS relapse following meningococcal C conjugate vaccine administration.[16] Similarly, Yildiz *et al* observed a higher relapse rate after the HBV vaccine was administered to some nephrotic children.[17]

Our study has some limitations. The effectiveness of the influenza vaccination varies annually based on the endemic strain. Our results are based only on its effect during one season, and the comparison group was from another season with a different strain of the endemic virus, so the results might not be replicable in other years. However, the significant beneficial effect we have observed after utilizing this vaccine at our center merits further multicenter trials in a larger cohort over a longer duration to ascertain the safety and efficacy of this vaccine in nephrotic children. Treating relapses requires the usage of steroids; this is detrimental to the health of the patients and must be avoided to the best of our abilities.

Conclusion

When compared with historic controls, the inactivated influenza virus vaccination in children with Nephrotic Syndrome has

proven to decrease the overall incidence of URI and associated relapses. The results further endorse the recommendation of annual influenza vaccinations in children with Steroid Sensitive Nephrotic Syndrome. Further studies with a larger cohort over different years are required to confirm our findings.

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