Open Access

Original Article

Association of Macrolide Use and Hearing Loss in Young Adults

Nauman Jamil, Maqbool Raza, Kamran Zamurrad Malik, Jahangir Ahmad Afridi, Shahzaib Shaukat, Fariha Shaheen

Department of ENT, Combined Military Hospital, Rawalpindi/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the association of Macrolide, use and hearing loss in young adults.
Study design: Quasi-experimental study.
Place and Duration of Study: ENT Head and Neck Surgery Department Combined Military Hospital, Rawalpindi, Pakistan from May 2023 to Oct 2023.
Methodology: A total of 54 patients fulfilling the selection criteria were enrolled after taking written informed consent and were divided into two Groups of 27 patients each. Group I consisted of patients with history of Macrolide use, Group II with history of Penicillin use. Sensorineural Hearing Loss (SNHL) was assessed in both Groups and findings were statistically analyzed.
Results: The mean age of the patients was 25.27±3.08 years, the mean duration of symptom was 7.33±2.71 days. There were 30(55.6%) males and 24(44.4%) females in the study. SNHL was reported in 6(11.1%) patients. In Group I, 4(14.8%) patients developed SNHL compared to 2(7.4%) patients in Group II. SNHL rate was higher in Macrolide Group.
Conclusion: The frequency of developing SNHL was found twice in patients who received Macrolide compared to Penicillin Group.

Keywords: Hearing loss, Macrolide, Penicillin, Sensorineural Hearing Loss.

How to Cite This Article: *Jamil N, Raza M, Malik KZ, Afridi JA, Shaukat S, Shaheen F. Association of Macrolide Use and Hearing Loss in Young Adults. Pak Armed Forces Med J 2025; 75(6): 1240-1244. DOI: https://doi.org/10.51253/pafmj.v75i6.12405*

INTRODUCTION

As children get older, hearing loss becomes more common, with 19% of children, adolescents, and young adults potentially affected. According to epidemiologic statistics, acquired causes account for 20% of these cases, hereditary factors for 23%, and idiopathic factors for 56% of them.[1] The large number of cases with unclear etiology suggests that there are widespread, continuing exposures occurring in the population that are not yet recognized and whose linkages are still being investigated.[2] Since sensorineural hearing loss (SNHL) can be irreversible, it is imperative to identify and be aware of any such exposures. This is especially true if the inciting factor is not stopped or if appropriate treatment is not started right once.[3]

Macrolides are among the most often prescribed medications for young adults, adolescents and children because they can be used to treat common ailments like sinusitis, otitis media, pneumonia, Helicobacter pylori or Campylobacter species infections of the gastrointestinal tract, and sexually transmitted diseases.[4] In addition to acting as antibiotics, Macrolides also have important immunomodulatory and antiviral actions. The use of Macrolide has increased over time in different countries. However, due to the widespread use of Macrolides, people are at risk for side effects like ototoxicity, gastrointestinal side effects, bacterial resistance and QTc prolongation.[5]

The relationship between the usage of Macrolides and ototoxicity has been examined in a number of earlier research.[6] Tinnitus and SNHL are two signs of ototoxicity. An analysis of four randomized controlled trials by the Cochrane review found that people who use Macrolides experience hearing loss more frequently.[7] Another comprehensive study found that even when given at recommended oral doses, SNHL is related to either oral or IV Macrolide use.[8] While some studies indicated that SNHL is permanent and dosage dependent, others discovered that it is reversible. In comparison to other antibiotics, Macrolides did not appear to carry a higher risk of SNHL, according to other larger-scale investigations, a retrospective cohort and a case-control study.[9] In a recent meta-analysis, there was no overall correlation between Macrolide antibiotics and SNHL (Odds ratio 1.30).[10] Previous studies on Macrolide usage and hearing loss had limitations and yielded contradictory results, with most studies consisting of small populations and

Correspondence: Dr Nauman Jamil, Department of ENT, Combined Military Hospital, Rawalpindi, Pakistan
Received: 01 Jul 2024; revision received: 12 Aug 2024; accepted: 13 Aug 2024

larger studies based on health claims data. Therefore, the current study aims to determine the association between the use of Macrolide and sensorineural hearing loss in young adults in Pakistan. The study will guide about an association between a commonly prescribed antibiotic and development of a serious complication, which if found to be significant can guide the treating physicians about reducing the use of Macrolide and detecting this complication earlier in order to prevent the development of further morbidity.

METHODOLOGY

It was a Quasi-experimental study. The study was carried out at the Combined Military Hospital, Rawalpindi, for a duration of six months i.e. from May 2023 to October 2023, after getting approval from the Ethical Review Committee (ERC number: 423). The sample size of 54 patients was calculated by keeping 95% confidence level, 5% margin of error, taking expected frequency of SNHL in young adults as 3.7%.[11] Non-probability consecutive sampling technique was used.

Inclusion Criteria: The study enrolled 54 patients of age 18 to 30 years, of both genders, and divided them by odd and even numbers into two Groups of equal numbers i.e. 27 in each Group. Group 1 consisted of individuals with a history of Macrolide exposure for any cause in the previous 6 months, Group II consisted of individuals with a history of Penicillin exposure for any condition in the previous 6 months.

Exclusion Criteria: Patients who were on one or more antibiotics at the time of enrollment, patients who had previously been diagnosed with any kind of hearing loss, and patients who had concurrent hospital stays were excluded.

After getting written informed consent from all patients who fulfilled the selection criteria, participants were enrolled in the study. A thorough history of the patients and clinical examination of all participants was done, and findings were noted down on a proforma. Patients were categorized as cases and controls. Cases were defined as those who had sensorineural hearing loss and control Groups comprised of healthy people without hearing loss. Hearing assessment was performed at baseline by pure tone audiometry (PTA). Pure tone audiometry (PTA) was used to establish the diagnosis of SNHL. PTA was classified as PTA0.25–8 ≥35 dB based on the Global Burden of Disease classification's cut-off for moderate hearing loss, which included 0.25 and 8 kHz.[12] In order to establish a 1:1 risk-set sampling, cases and controls were matched according to age, gender, and the duration since the prescription date. We identified prescriptions of Macrolide for Erythromycin, Azithromycin, Telithromycin, Clarithromycin and Fidaxomicin, excluding topical medication, in order to ascertain the status of Macrolide exposure. Because the Penicillin class of medications is expected to have no connection with hearing loss, it was chosen as the control exposure. Penicillin G potassium, Cloxacillin, Dicloxacillin, Carbenicillin, Indanyl sodium, Oxacillin, Phenoxymethyl Penicillin, Ampicillin, Ampicillin-sulbactam, and Amoxicillin were among the antibiotics in the Penicillin Group. Findings were noted down on the proforma and were subjected to statistical analysis.

The data was analyzed through Statistical Package for social sciences (SPSS) version 25.0. Quantitative data such as age, duration of symptoms and PTA values were presented as Mean±SD. Qualitative data such as age Group, gender, smoking history, symptom duration and type of exposure (Macrolide or Penicillin) were presented as frequency and percentages. The frequency between exposure status and the presence of hearing loss was examined by using the chi-square test. The p value ≤ 0.05 was considered as significant.

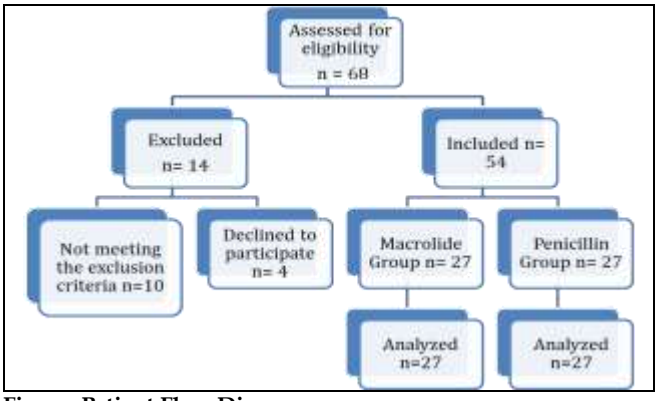

Figure: Patient Flow Diagram

RESULTS

A total of 54 patients were enrolled. The mean age of the patients was 25.27±3.08 years, the mean duration of symptom was 7.33±2.71 days and the mean PTA value was 27.81±8.57 dB (Table-I). With respect to age Group, there were 30(55.6%) patients between 18 to 25 years of age and 24(44.4%) patients between the age of 26 to 30 years. There were

30(55.6%) males and 24(44.4%) females in the study. History of smoking was present in 15(27.8%) patients. SNHL was reported in 6(11.1%) patients. The duration of symptoms was ≤7 days in 28(51.9%) patients and >7 days in 26(48.1%) patients (Table-II). Among the Macrolide user Group, 4(14.8%) patients had SNHL compared to 2(7.4%) patients of SNHL in the Penicillin user Group. The *p*-value of 0.185 suggests that the difference in hearing loss frequency between the two Groups is not statistically significant (Table-III).

Table-I: Descriptive Statistics in Study Participants (n=54)

Variables	Mean±Standard deviation
Age (in years)	25.27±3.08
Duration of Symptoms (in days)	7.33±2.71
Pure tone audiometry (PTA) value (in dB)	27.81±8.57

Table-II: Frequency Distribution of Qualitative Variables in Study Participants (n=54)

Variables	Frequency (Percentage)
Age Group	
18 to 25 years	30(55.6%)
26 to 30 years	24(44.4%)
Gender	
Male	30(55.6%)
Female	24(44.4%)
History of Smoking	
Yes	15(27.8%)
No	39(72.2%)
Symptoms Duration	
≤7 days	28(51.9%)
>7 days	26(48.1%)
Type of exposure	
Macrolide	6(11.1%)
Penicillin	48(88.9%)

DISCUSSION

The current study results showed that the rate of developing SNHL was twice in the patients who had exposure to Macrolide compared to the development of SNHL in the Penicillin Group, denoting that the risk of hearing loss was increased with Macrolide exposure.

Table-III: Hearing Loss Frequency in Macrolide and Penicillin Exposed Groups (n=54)

Study Groups	Hearing loss Present n (%)	Hearing loss Absent n (%)	Total	*p*-value
Macrolide use	4(14.8%)	23(85.2%)	27	0.185
Penicillin use	2(7.4%)	25(92.6%)	27	

One of the most often prescribed drugs for young patients and children is Macrolide.[13] According to surveys of randomly chosen households, 0.6% of children had used this drug just in the last week. Additionally, there may be an increase in the usage of Macrolides among children, teenagers, and young adults between the ages of 4 and 18. Due to this widespread use, the potential link with public health may still be significant even if just a small percentage of Macrolide users have SNHL. Because there are more than 54 million prescriptions for Macrolides, a risk difference of just 0.7% is expected to affect 7000 people for every 1 million prescriptions, or 378,000 patient's annually.[14] Additionally, the therapeutic window might be constrained if SNHL develops suddenly. When steroid treatment is advised, it might be best administered during the first 14 days following hearing loss.[15] The suspected agent should be stopped as soon as possible. Therefore, early detection and clinician and parent knowledge are crucial. The rare development of SNHL in adults with concomitant illnesses has been associated with intravenous or high-dose Macrolide therapy; however, there have been little research on the auditory effects of oral outpatient dosage for children, adolescents, and young adults.[16]

Our study compared the rate of development of SNHL among Macrolide and Penicillin users and found that the rate of developing SNHL was twice in patients who received Macrolide compared to those who received Penicillin. Dabekausen *et al*., in a meta-analysis revealed that patients with SNHL had higher probabilities of receiving a prescription for a Macrolide than a prescription for Penicillin (adjusted odds ratio, 1.31) and when diagnosis and testing took place more than 180 days after antibiotic exposure, there were substantially higher probabilities of being exposed to Macrolides than Penicillin (adjusted odds ratio, 1.79).[14] Alsowaida *et al*., in a meta-analysis revealed that the frequency of SNHL was higher in patients who received Macrolide compared to control, however, there was no significant association between Macrolide usage and hearing loss as was indicated by an odds ratio of 1.2.[17] Lieu and Rybak revealed that SNHL occurred in 78 patients who were given Macrolide and majority had SNHL of reversible nature.[18] Haffernen *et al*., revealed that 7% patients developed SNHL after taking Macrolide.[19] These findings support our study findings that patients who received Macrolide developed SNHL, however,

contradictory evidence has been yielded by previous studies in terms of association between Macrolide usage and SNHL.

The strength of our study is that many of the studies conducted previously were patient based and very few population-based studies have been carried out and thus our study is a population-based study conducted locally which can provide better results. After literature research there is no evidence based study in Pakistan relating to Macrolide usage and SNHL however Atif *et al*., highlighted the role of Streptomycin in Multidrug resistant Tuberculosis.[20] Furthermore, we used pure tone audiometry rather than subjective documentation of SNHL, thus reducing the risk of bias.

LIMITATIONS OF STUDY

There were certain limitations to the study. The association of Macrolide with hearing loss was only assessed in patients who had otitis media and it could not be established if the use of Macrolide for other indications similarly led to significant association with hearing loss or not.

CONCLUSIONS

The current study concluded that the rate of developing SNHL was twice in patients who received Macrolide compared to the rate of developing hearing loss among patients who received Penicillin. Clinicians should be aware of this harmful effect of medicine, particularly when Macrolide antibiotics are used long-term, and further research is required to validate the relationship and explore the pathophysiological mechanism. Future studies must be carried out on a larger sample size for validating the findings of current study.

ACKNOWLEDGEMENTS

We would like to thank all of our seniors and our colleagues who helped us in compiling this study, helped in collecting data.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

NJ & MR: Data acquisition, data analysis, critical review, approval of the final version to be published.

KZM & JAF: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SS & FS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Davis AC, Hoffman HJ. Hearing loss: rising prevalence and impact. Bull World Health Organ 2019; 97(10): 646. https://doi:10.2471/BLT.19.224683
2. Michels TC, Duffy MT, Rogers DJ. Hearing loss in adults: differential diagnosis and treatment. Am Fam physician 2019; 100(2): 98-108. https://doi.org/10.1016/S0924-8579(01)00319-7
3. Van-Beeck Calkoen EA, Engel M, Van-de Kamp J, Yntema H, Goverts S, Mulder M, et al. The etiological evaluation of sensorineural hearing loss in children. Eur J Pediatr 2019; 178: 1195-205. https://doi.org/10.1007/s00431-019-03379-8
4. Williams J. Evaluation of the safety of macrolides. Int J Antimicrob Agents 2001; 18: 77-81. https://doi.org/10.1016/S0924-8579(01)00399-5
5. Altenburg J, De-Graaff C, Van-der Werf T, Boersma W. Immunomodulatory effects of macrolide antibiotics–part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. Respiration 2010; 81(1): 75-87. https://doi.org/10.1159/000320320
6. Li H, Liu D-H, Chen L-L, Zhao Q, Yu Y-Z, Ding J-J, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother 2014; 58(1): 511-517. https://doi.org/10.1128/aac.02067-13
7. Hansen MP, Scott AM, McCullough A, Thorning S, Aronson JK, Beller EM, et al. Adverse events in people taking macrolide antibiotics versus placebo for any indication. Cochrane Database System Rev 2019; (1): CD011825. https://doi.org/10.1002/14651858.CD011825.pub2
8. Coulston J, Balaratnam N. Irreversible sensorineural hearing loss due to clarithromycin. Postgrad Med J 2005; 81(951): 58-59. https://doi.org/10.1136/pgmj.2004.020412
9. Ress BD, Gross EM. Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity: a case report. Ann Otol Rhinol Laryngol 2000; 109(4): 435-437. https://doi.org/10.1177/000348940010900416
10. Lindeborg MM, Jung DH, Chan DK, Mitnick CD. Prevention and management of hearing loss in patients receiving ototoxic medications. Bull World Health Organ 2022; 100(12): 789. http://doi:10.2471/BLT.21.286823
11. Naz E, Saqulain G, Mumtaz N, Babur MN. A Hospital based study on sudden sensorineural Hearing Loss: It's audiological characteristics and prevalence. Pak J Med Sci 2021; 37(4): 1133. http://doi:10.12669/pjms.37.4.3851
12. Vanoverschelde A, Oosterloo BC, Ly NF, Ikram MA, Goedegebure A, Stricker BH, et al. Macrolide-associated ototoxicity: a cross-sectional and longitudinal study to assess the association of macrolide use with tinnitus and hearing loss. J Antimicrob Chemother 2021; 76(10): 2708-2716. https://doi.org/10.1093/jac/dkab232
13. Etminan M, Westerberg BD, Kozak FK, Guo MY, Carleton BC. Risk of sensorineural hearing loss with macrolide antibiotics: A nested case-control study. Laryngoscope 2017; 127(1): 229-232. https://doi.org/10.1002/lary.26190
14. Dabekaussen KF, Andriotti T, Ye J, Prince AA, Nguyen LL, Feng AY, et al. Association of outpatient oral macrolide use with sensorineural hearing loss in children, adolescents, and young adults. JAMA Otolaryngol Head Neck Surg 2022; 148(9): 820-827. http://doi:10.1001/jamaoto.2022.1293

15. Wong EH, Porter JD, Edwards MR, Johnston SL. The role of macrolides in asthma: current evidence and future directions. Lancet Respirat Med 2014; 2(8): 657-670. https://doi.org/10.1016/S2213-2600(14)70107-9
16. Askari M, Khezri M, Zoghi G. Introducing a Novel Combination Therapy with Macrolides for the Treatment of Chronic Rhinosinusitis: A Randomized Controlled Trial. Iran J Med Sci 2022; 47(6): 533. http://doi:10.30476/IJMS.2021.91813.2303
17. Alsowaida YS, Almulhim AS, Oh M, Erstad B, Abraham I. Sensorineural hearing loss with macrolide antibiotics exposure: a meta-analysis of the association. Int J Pharm Pract 2021; 29(1): 21-28. https://doi.org/10.1111/ijpp.12670
18. Lieu JE, Rybak L. Possibility of Macrolides Causing Hearing Loss in Children—What Did You Say? JAMA Otolaryngol Head Neck Surg 2022; 148(9): 827-829. http://doi:10.1001/jamaoto.2022.1292
19. Heffernan CB, McKeon MG, Molony S, Kawai K, Stiles DJ, Lachenauer CS, et al. Does clarithromycin cause hearing loss? A 12-year review of clarithromycin therapy for nontuberculous mycobacterial lymphadenitis in children. Ann Otol Rhinol Laryngol 2018; 127(10): 687-693. https://doi.org/10.1177/0003489418788112
20. Rafique A, Dastgir M, Jamalullah M, Maqbool S, Basher S, Rashid M et al. Streptomycin associated hearing loss in patients treated for multidrug resistant tuberculosis. Isra Med J 2012; 4(3): 139-142.