ORIGINAL ARTICLE

Role of Prophylactic Antibiotics in Preventing Stroke-Associated Pneumonia in Patients with Ischemic Stroke

Muhammad Jawad Aslam[1*], Muhammad Amir[2], Tahir Mukhtar Sayed[3], Asif Hashmat[4], Maryam Hussain[2], Minahil Fatima[5]

ABSTRACT

Objective: To compare the frequency of stroke-associated pneumonia in patients given prophylactic antibiotics versus those not given prophylactic antibiotics.

Study Design: Comparative Cross-sectional study.

Place and Duration of Study: The study was carried out at the Department of Internal Medicine, Combined Military Hospital (CMH), Peshawar, Pakistan from 1st August 2022 to 31st January 2023.

Methods: We included 250 ischemic stroke patients and divided them into groups A, "Prophylactic group," and B, "no prophylactic antibiotics group." Patients were assessed at 7 days after admission for presence of "stroke associated pneumonia (SAP)" through clinical examination and chest X-rays. Data were analyzed using a statistical package for social sciences 22. For qualitative variables, frequency and percentages were used, whereas for quantitative data, the median (IQR) was used as the data were not normally distributed and contained outliers; using the median and IQR can be more appropriate for describing the central tendency and spread of the data compared to the mean and standard deviation.

Results: In our study, the median age of the patients was 68(46-83) years. 61 (24.40%) of the patients were male while 189(75.60%) were female. The median BMI was 31 (19-44) kg/m2. Diabetes was present in 123 (49.20%) patients and 96(38.40%) had hypertension. We found that in the the "prophylactic antibiotics" group (A), 9 (7.20%) patients developed SAP, while in the "no prophylactic antibiotics" group (B) frequency of SAP was 34 (27.20%) (p< 0.001).

Conclusion: Prophylactic antibiotics used in "ischemic stroke" patients provide better outcomes by reducing the incidence of "stroke-associated pneumonia". Therefore, it should be given to all patients admitted to the hospital with ischemic CVA.

Keywords: *Antibiotic Prophylaxis, Ischemic Stroke, Pneumonia*.

How to cite this: *Aslam MJ, Amir M, Sayed TM, Hashmat A, Hussain M, Fatima M.Role of Prophylactic Antibiotics in Preventing Stroke Associated Pneumonia in Patients with Ischemic Stroke. Life and Science. 2024; 5(1): 83-88. doi: http://doi.org/10.37185/LnS.1.1.465*

[1]*Department of Medicine/Neurology*[4]
Combined Military Hospital (CMH), Sargodha, Pakistan
[2]*Department of Pulmonology and Neurology*
Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan
[3]*Department of Medicine*
Akhtar Saeed Medical College, Rawalpindi, Pakistan
[5]*Department of Medicine*
HITEC Institute of Medical Sciences, Rawalpindi, Pakistan
Correspondence:
Dr. Muhammad Jawad Aslam
Department of Medicine
Combined Military Hospital (CMH), Sargodha, Pakistan
E-mail: Jawad_488@yahoo.com
Funding Source: NIL; Conflict of Interest: NIL
Received: Aug20, 2023; Revised: Oct 12, 2023
Accepted: Nov 08, 2023

Introduction

Stroke or "cerebrovascular accident (CVA)" is one of the most commonly encountered neurological emergencies that has the potential to cause disability, financial burden due to health care costs, a spectrum of morbidities, and even death in severe cases. It is diagnosed with the help of computed tomography (CT) scan of the head and clinically is defined by the "presence of focal neurological deficit of new-onset which is vascular in origin and persists for a period of ≥ 24 hours".[1] Based on radiological findings, stroke has been primarily classified into two major types. One is "ischemic stroke," which involves

disruption in the cerebral circulation secondary to blockage in the supplying vessel. Second is "hemorrhagic stroke," which occurs due to disruption in the vascular integrity leading to leakage of blood into the brain matter and is sub-classified as "intra-cerebral hemorrhage (ICH)" and "sub-arachnoid hemorrhage (SAH)".[2] Amongst these varieties of stroke, "ischemic stroke" constitutes the major burden of stroke on the health care systems.[3]

The propensity of developing an acute event of "Cerebrovascular accident (CVA)" can be enhanced by the presence of a wide range of contributors, which are classified as "non-modifiable" factors (older age, ethnicity of a person and their gender), and "modifiable" factors, (being overweight, not getting enough exercise, leading a sedentary lifestyle, eating unhealthy foods and having co-existent diabetes or hypertension).[4] Regardless of the risk factors, the life of a patient with stroke is at risk not only by virtue of the phenomenon of stroke itself but also due to its associated complications. Infections constitute a major chunk of these associated complications, which prove to be a significant cause of mortality and morbidity in such patients.[5] One such infection that is not only life-threatening but also one of the most prevalent is "stroke-associated pneumonia," which occurs due to repeated micro-aspirations of the gastric contents that result secondary to disordered swallowing and coughing function of the patient secondary to stroke.[6] Therefore, it is of utmost importance to administer interventions that can help reduce its incidence. One such intervention is the use of prophylactic antibiotics. However, it has been observed in previous literature that when it comes to amusing antibiotic prophylaxis preventing the incidence of "stroke-associated pneumonia," results have been highly variable, with some studies reporting no benefit of this practice. The two major trials in this regard include the PASS trial and STROKE-INF trials.[7,8] The former study encompasses all stroke-related infections, while the latter assesses the risk of pneumonia in stroke patients with dysphagia. On the other hand, there are also published studies that provide evidence of a reduction in the frequency of "stroke-associated pneumonia" and infections with prophylactic administration of antibiotics.[9]

Owing to such discrepancy in the previous literature, we aimed to conduct this study with the purpose of determining role of prophylactic antibiotics focusing on the prevention of "stroke associated pneumonia", in a Pakistani hospital, using a readily available third generation cephalosporin - Ceftriaxone. Results from our study will provide insight into the usefulness of this practice and its efficacy in improving the outcomes of stroke patients.

Methods

This comparative study was conducted at the Department of Internal Medicine, Combined Military Hospital (CMH), Peshawar, Pakistan from 1st August 2022 to 31st January 2023 after obtaining approval from the ethical review committee of the Combined Military Hospital, Peshawar, Pakistan, held on 13th July 2022 vide letter no: ERB Reg. #: 0367/22/psc) For calculation of sample size, we used WHO sample size calculator 2.2b (Hypothesis testing for two population proportions) using formula.[10]

$$n = \frac{\left\{Z\frac{1-\alpha}{2}\sqrt{2P(1-P)} + Z(1-\beta)\sqrt{P1(1-P1) + P2(1-P2)}\right\}_2}{(P1-P2)_2}$$

To calculate sample size, we used a 5% level of significance, 80% power of the test, anticipated population proportion of post-stroke pneumonia in the preventive antibiotics group of (3/39) 7.7%, and anticipated population proportion of post-stroke pneumonia in the control group of (8/40) 20%.[11] Based on these our calculated sample size was 250 (125 patients in each group).

Inclusion criteria: We included adult patients, aged 35-85 years, either of the male or female genders, having CT-proven "ischemic stroke" with absent gag reflex and presentation within 24 hours of onset of stroke.

Exclusion criteria: We excluded patients who had a hemorrhagic stroke, mechanically ventilated patients, patients with pre-existing pulmonary pathology, and those with clinical-radiological evidence of pre-existing infection.

After patient selection through non-probability sampling, we recorded baseline characteristics of our patients, including age, gender, body mass index (BMI), presence of diabetes (HbA1C% ≥ 6.5%), and hypertension (≥ 130/80 mmHg). Once recorded,

patients were randomly divided into two equal groups (each consisting of 125 patients). In group A, or the "prophylactic antibiotics group," patients were empirically given injections of Ceftriaxone 1g IV twice daily for a period of 7 days in addition to adequate posturing during and after feeding through nasogastric tube and chest physiotherapy, while in group B or "no prophylactic antibiotics group" patients were only managed by adequate posturing during and after feeding through nasogastric tube and chest physiotherapy. All the patients during the study period were monitored for their vitals every six hours and were also provided standard treatment with IV fluids, anti-platelet drugs [tablet Disprin (aspirin) 300mg stat followed by Coated aspirin 75mg once daily], and statin therapy [tablet Lipiget (atorvastatin) 10mg daily at night]. On the 8th day when there was the completion of treatment, patients were assessed for the presence of "stroke associated pneumonia," which was defined as "pulmonary infection within 7 days of stroke".[12] Presence of pulmonary infection was ensured by the presence of coarse crackles on chest auscultation along with presence of infiltrates on chest X-rays.

The statistical package for social sciences (SPSS) version 22 software was used for statistical analysis of the data. The normality of the test was checked using the Shapiro-Wilk test, which showed that age and BMI were not normally distributed. For qualitative variables, frequency and percentages were used, whereas for quantitative data, median (IQR) was used. Qualitative variables (gender, presence of diabetes, hypertension, and stroke-associated pneumonia) were compared between groups with the use of a chi-square test. Quantitative variable (age and BMI) were compared between groups using Mann-Whittney U-test. A *p*-value of ≤0.05 was considered significant.

Results

In our study, a total of 250 patients were included. In our study, the median age of the patients was 68 (46-83) years. In our study, 61 (24.40%) of the patients were male, while 189 (75.60%) of the study participants were female. The median BMI of the study population was 31 (19-44) kg/m^2. Diabetes was present in 123 (49.20%) patients and 96 (38.40%) had hypertension. These baseline characteristics are tabulated below in Table 1.

Table 1: Baseline characteristics (n = 250)

Characteristic	Value (n = 250)
Median age (years)	68 (46-83)
Gender n (%)	
Male	61 (24.40)
Female	189 (75.60)
Mean BMI (kg/m^2)	31 (19-44)
Diabetes n (%)	
Yes	123 (49.20)
No	127(50.80)
Hypertension n (%)	
Yes	96 (38.40)
No	154 (61.60)

We compared these baseline characteristics between our study groups. The median age in "prophylactic antibiotics" group (A) was 68 (46-83) years while in "no prophylactic antibiotics" group (B) it was 68 (47-83) years, (p = 0.955). Median BMI in the "prophylactic antibiotics" group (A) was 30.30 (19.10 - 44.00) kg/m2, and in the "no prophylactic antibiotics" group (B), it was 31.00(23.40 – 44.00) kg/m^2, (p = 0.406). There was no significant difference between groups in terms of gender distribution (p = 0.462), presence of diabetes (p = 0.704), and presence of hypertension (p = 0.603). This comparison is tabulated below in Table 2.

Upon comparison of the frequency of "stroke associated pneumonia (SAP)" between groups, we found that in "prophylactic antibiotics" group A, 9 (7.20%) patients developed SAP while in "no prophylactic antibiotics" group B frequency of SAP was 34 (27.20%), (p < 0.001). This is tabulated below in Table 3.

Table 2: Comparison of baseline characteristics between groups (n = 250)

Variables	Group A (n = 125) Prophylactic antibiotics		Group B (n = 125) No prophylactic antibiotics		*p*-value
Median age (years)	68 (46-83)		68 (47-83)		0.95
Gender	Male	28 (22.40)	Male	33 (26.40)	0.46
	Female	97 (77.60)	Female	92 (73.60)	
Mean BMI (kg/m^2)	30.30 (19.10 - 44.00)		31.00 (23.40 – 44.00)		0.40
Diabetes	Yes	60 (48.00)	Yes	63 (50.40)	0.70
	No	65 (52.00)	No	62 (49.60)	
Hypertension	Yes	49 (39.20)	Yes	50 (40.00)	0.60
	No	76 (60.80)	No	75 (60.00)	

Table 3: Comparison of frequency of SAP between groups (n = 250)

Parameter	Group A(n = 125) Prophylactic antibiotics	Group B (n = 125) No prophylactic antibiotics	*P*-value
Stroke Associated Pneumonia (SAP)	9 (7.20%)	34 (27.20%)	< 0.001

Discussion

There are around 1200 cases of stroke for every 100,000 people in Pakistan with only one specialist neurologist available for the treatment of every million people, making stroke a major health concern in the country.[13,14] Additionally, stroke related complications that contribute to additional mortality in stroke patients are also a cause of concern for treating physicians.[15,16] Our study focused primarily on one of the most commonly encountered complication of stroke, i.e., "stroke associated pneumonia (SAP)" which is one of the major reason of in-hospital mortality of a recovering stroke patients.[17,18] In our study, we found that most of the patients who had stroke belonged to middle to older age with an unhealthy range of BMI. This may be due to strong association between unhealthy BMI and chance of having an acute attack of CVA.[19,20] Contrary to norm, our study found that most of the patients were women while literature exhibits that majority of patients who have stroke are of male gender.[21,22] The frequency of diabetes and hypertension was quite high among study population. This concurs with the fact that both these conditions accentuate the propensity of developing a stroke.[23,24]

In terms of use of prophylactic antibiotics and prevention of "stroke associated pneumonia (SAP)", current study have exhibited very promising results in favor of practicing administration of empirical antibiotics as prophylaxis against SAP in patients who are admitted at hospital with an ischemic stroke. In present study, difference in frequency of SAP between "prophylactic antibiotics group" (7.20%) and "no prophylactic antibiotics group" (27.20%) was of statistical significance; with much lower frequency reported in "prophylactic antibiotics" group. Findings of present study were in congruence with what was observed by Zheng et al. who also reported a significantly less frequency of SAP among those who were given anti-microbial prophylaxis.[25] In addition, Sluis et al. also found similar results as of current study with lesser pneumonia events with use of antibiotics, in particular ceftriaxone.[26] Similarly, Harms et al. reported that frequency of SAP was lower in stroke patients given preventive antibiotics (7.7%) as compared to those not given preventive antibiotics (20%).[11] Concurrently, findings of Badve et al. also were in sync with results of present study.[27] On the other hand, Kalra et al. concluded that there was no additional benefit of regular prophylactic use of anti-microbial agents in terms of preventing "stroke associated pneumonia (SAP)" and therefore should not be practiced and reported that frequency of SAP in patients given preventive antibiotics was in fact higher (13%) as compared to those not given any prophylactic cover of antibiotics (10%).[8] Similarly, Kishore et al. and Vermeij et al. also found no additional benefit in use of preventive antibiotics among stroke patients to avoid aspiration and subsequent pneumonia.[28,29] Concomitantly, another

study found no difference in frequency of pneumonia in stroke patients who were given antibiotics (13%) as compared to those not given antibiotics (10%).[30]

There were few limitations of present study including study confined to single center, limited duration of follow up and limited sample size. Based on the finding of present study, it is strongly recommend that all patients who are admitted in hospital after an acute event of CVA should be given prophylaxis with empirical antibiotics to prevent "stroke associated pneumonia (SAP)". In addition, based on discrepancies in present study and previous literature, it is also recommend to conduct further studies with larger sample sizes to draw a conclusive evidence in favor or against this practice.

Conclusion

In conclusion, prophylactic antibiotics used in "ischemic stroke" patients provide better outcomes by reducing the incidence of "stroke-associated pneumonia". Therefore, it should be given to all patients admitted to the hospital with ischemic CVA.

REFERENCES

1. Murphy SJ, Werring DJ. Stroke: causes and clinical features. Medicine. 2020; 48: 561-6. doi: 10.1016/j.mpmed.2020.06.002
2. Namaganda P, Nakibuuka J, Kaddumukasa M, Katabira E. Stroke in young adults, stroke types and risk factors: a case control study. BMC Neurology. 2022; 22: 335. doi: 10.1186/s12883-022-02853-5
3. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. International Journal of Molecular Sciences. 2020; 21: 7609. doi: 10.3390/ijms21207609
4. Koltsova EA, Petrova EA, Borshch YV. Obzorfaktorovriskainsul'ta [An overview of risk factors for stroke]. ZhurnalNevrologii I PsikhiatriiImeni S.S. Korsakova. 2022; 122: 12-9. doi: 10.17116/jnevro202212212212
5. Ghelani DP, Kim HA, Zhang SR, Drummond GR, Sobey CG, De Silva TM. Ischemic stroke and infection: A brief update on mechanisms and potential therapies. Biochemical Pharmacology 2021; 193: 114768. doi: 10.1016/j.bcp.2021.114768
6. Assefa M, Tadesse A, Adane A, Yimer M, Tadesse M. Factors associated with stroke associated pneumonia among adult stroke patients admitted to university of Gondar hospital, Northwest Ethiopia. Scientific Reports. 2022; 12: 12724. doi: 10.1038/s41598-022-14656-2
7. Westendorp WF, Vermeij JD, Zock E, Hooijenga IJ, Kruyt ND, Bosboom HJ, et al. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. Lancet. 2015; 385: 1519-26. doi: 10.1016/S0140-6736(14)62456-9
8. Kalra L, Irshad S, Hodsoll J, Simpson M, Gulliford M, Smithard D, et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. Lancet. 2015; 386: 1835-44. doi: 10.1016/S0140-6736(15)00126-9
9. Wang Q, Wu ZY, Tang HL, Yi ZM, Zhai SD. The efficacy and safety of prophylactic antibiotics for post-acute stroke infection: A systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2023; 89: 946-55. doi: 10.1111/bcp.15646
10. Naing L, Nordin RB, Abdul Rahman H, Naing YT. Sample size calculation for prevalence studies using Scalex and ScalaR calculators. BMC Medical Research Methodology. 2022; 22: 1-8. doi: 10.1186/s12874-022-01694-7
11. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. PLoS One. 2008; 3: e2158. doi: 10.1371/journal.pone.0002158
12. Chen Y, Yang H, Wei H, Chen Y, Lan M. Stroke-associated pneumonia: A bibliometric analysis of worldwide trends from 2003 to 2020. Medicine. 2021; 100: e27321. doi: 10.1097/MD.0000000000027321
13. Sherin A, Ul-Haq Z, Fazid S, Shah BH, Khattak MI, Nabi F. Prevalence of stroke in Pakistan: Findings from Khyber Pakhtunkhwa integrated population health survey (KP-IPHS) 2016-17. Pakistan journal of medical sciences. 2020; 36: 1435-40. doi: 10.12669/pjms.36.7.2824
14. Farooq A, Venketasubramanian N, Wasay M. Stroke care in Pakistan. Cerebrovascular Diseases Extra. 2021; 11: 118-21. doi: 10.1159/000519554
15. Asgedom SW, Gidey K, Gidey K, Niriayo YL, Desta DM, Atey TM. Medical complications and mortality of hospitalized stroke patients. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association. 2020; 29: 104990. doi: 10.1016/j.jstrokecerebrovasdis.2020.104990
16. Tareke AA, Abate MG, Alem A, Alamneh YM, Alamneh AA, Deml YA, et al. Magnitude and predictors of in-hospital stroke mortality in Ethiopia: a systematic review and meta-

analysis. Stroke Research and Treatment. 2022; 2022: 7202657. doi: 10.1155/2022/7202657

17. Hashim H, Shahid L, Bajwa D, Usman R, Ahmed SS, Khokhar M. Prevalence of stroke associated pneumonia in stroke patients. Pakistan Journal of Medical and Health Sciences. 2022; 16: 590-2. doi: 10.53350/pjmhs221610590
18. Patel UK, Kodumuri N, Dave M, Lekshminarayanan A, Khan N, Kavi T, et al. Stroke-associated pneumonia: a retrospective study of risk factors and outcomes. The Neurologist. 2020; 25: 39-48. doi: 10.1097/NRL.0000000000000269
19. Shiozawa M, Kaneko H, Itoh H, Morita K, Okada A, Matsuoka S, et al. Association of body mass index with ischemic and hemorrhagic stroke. Nutrients. 2021; 13: 2343. doi: 10.3390/nu13072343
20. Song DK, Hong YS, Sung YA, Lee H. Body mass index and stroke risk among patients with diabetes mellitus in Korea. PLoS One. 2022; 17: e0275393. doi: 10.1371/journal.pone.0275393
21. Appelros P, Åsberg S. Sex differences in stroke. Handboom of Clinical Neurology 2020; 175: 299-312. doi: 10.1016/B978-0-444-64123-6.00021-7
22. Peters SAE, Carcel C, Millett ERC, Woodward M. Sex differences in the association between major risk factors and the risk of stroke in the UK Biobank cohort study. Neurology. 2020; 95: e2715-e26. doi: 10.1212/WNL.0000000000010982
23. Mosenzon O, Cheng AY, Rabinstein AA, Sacco S. Diabetes and stroke: what are the connections? Journal of Stroke. 2023; 25: 26-38. doi: 10.5853/jos.2022.02306
24. Kim TH, Yang PS, Yu HT, Jang E, Shin H, Kim HY, et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. European Heart Journal. 2019; 40: 809-9. doi: 10.1093/eurheartj/ehy877
25. Zheng F, Spreckelsen NV, Zhang X, Stavrinou P, Timmer M, Dohmen C, et al. Should preventive antibiotics be used in patients with acute stroke? A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2017; 12: e0186607. doi: 10.1371/journal.pone.0186607
26. Sluis WM, Westendorp WF, van de Beek D, Nederkoorn PJ, van der Worp HB. Preventive ceftriaxone in patients at high risk of stroke-associated pneumonia. A post-hoc analysis of the PASS trial. PLoS One. 2022; 17: e0279700. doi: 10.1371/journal.pone.0279700
27. Badve MS, Zhou Z, Anderson CS, Hackett ML. Effectiveness and safety of antibiotics for preventing pneumonia and improving outcome after acute stroke: systematic review and meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 2018; 27: 3137-47. doi: 10.1016/j.jstrokecerebrovasdis 2018.07.001
28. Kishore AK, Jeans AR, Garau J, Bustamante A, Kalra L, Langhorne P, et al. Antibiotic treatment for pneumonia complicating stroke: Recommendations from the pneumonia in stroke consensus (PISCES) group. European Stroke Journal. 2019; 4: 318-28. doi: 10.1177/2396987319851335
29. Vermeij JD, Westendorp WF, Dippel DW, van de Beek D, Nederkoorn PJ. Antibiotic therapy for preventing infections in people with acute stroke. Cochrane Database of Systemic Reviews 2018; 1: CD008530. doi: 10.1002/14651858.CD008530.pub3
30. Schwarz S. Prophylactic antibiotic therapy for preventing poststroke infection. Neurotherapeutics. 2016; 13: 783-90. doi: 10.1007/s13311-016-0466-y

Authors Contribution

MJA: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proof reading

MA: Data collection, data analysis, results and interpretation, manuscript writing and proof reading

TMS: Idea conception, manuscript writing and proof reading

AH: Idea conception, study designing, data analysis, results and interpretation, manuscript writing and proof reading

MH: Data collection, data analysis, results and interpretation, manuscript writing and proof reading

MF: Data collection