

Choice of antibiotics prescribed following periodontal flap surgery and its influence on healing

To,

The Editor,

I would like to submit our manuscript entitled "Choice of antibiotics prescribed following periodontal flap surgery and its influence on healing" for possible consideration. With the submission of the article, I in capacity of corresponding author undertake that;

- All the authors listed in this article have made substantial contributions to the conception or design of the work; or the acquisition, analysis and interpretation of the data for the work; and drafting the work or reviewing it critically for important intellectual content; and final approval of the versic of manuscript to be published.
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Abstract

Background: Periodontitis is an inflammatory disease which affects the periodontium and periodontal flap surgeries are done to eliminate the resultant pocket formation and induce healing. Post flap surgery, antibiotics may or may not be prescribed, depending on the situation. Usefulness of postoperative antibiotics on postoperative healing is inconclusive.

Aim: The aim of the study was to evaluate the prevalence of antibiotic usage in patients undergoing flap surgery, choice of antibiotics and their influence on postoperative healing.

Material and method: The data collection was done with the digital case records of a dental hospital. Data collected from case records of all flap surgeries from June 2019 to March 2020. Out of the patients with periodontitis, 701 patients who underwent flap surgery were included in the study. The data retrieved included patients details, site of surgery, the antibiotics prescribed and the post operative healing and complications.

Results: Antibiotics were prescribed for 93.58% of surgeries. The most commonly prescribed antibiotic was Amoxicillin. Site of surgery and gender did not have any significant influence on the antibiotic usage ($p > 0.05$). No significant difference was seen in the healing index between flap surgeries done with or without antibiotics prescribed

($p > 0.05$). Postoperative complications were very few and antibiotics usage did not have any significant influence on the same.

Conclusion: It can be concluded that antibiotics are frequently used postoperatively in flap surgeries but do not have much influence on healing or postoperative complication.

Clinical significance: This study reports the uselessness of the postoperative antibiotic usage after periodontal flap surgery.

Keywords: Antibiotics, Complications, Flap surgery, Postoperative healing.

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INTRODUCTION:

Periodontitis is an inflammatory disease of supporting tissues of the teeth caused by a group of microorganisms, which result in progressive destruction of the periodontal ligament and the alveolar bone, (Ramesh, Ravi and Kaarthikeyan, 2017) resulting in periodontal pocket formation, gingival recession or both. It results from interplay of bacterial infection and host response, and further modified by environmental, risk factors and genetic susceptibility. (Ramesh *et al.*, 2016),³ Periodontitis is a multifactorial disease characterized by an inflammation of the periodontal tissue mediated by the host, which is associated with dysbiotic plaque biofilms can have systemic implications as well. (4,5)

Bacteria is the primary etiological agent known for the cause of periodontitis. Over 250 species are capable of colonizing in the mouth. But, the most common organisms responsible are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus Actinomycetemcomitans*, as well as treponemes. (6,7) The development of gingivitis and periodontitis can be divided into a series of stages: initial, early, established, and advanced lesions. The initial lesion begins 2–4 days after the accumulation of the microbial plaque.^(8,9) The early injury develops within 4–10 days. Subsequently, the established lesion develops within 2–3 weeks. . Finally, in the advanced lesion, plasma cells continue to predominate as the architecture of the gingival tissue is disturbed, together with the destruction of the alveolar bone and periodontal ligament.^(10,11,12) Macrophages are an important source of proinflammatory and potentially destructive molecules for tissues, such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), MMP, and prostaglandin E2, which play an important role and are elevated in the gingival tissue and in the gingival crevicular fluid of patients with chronic periodontitis.^(13,14,15) Since the periodontitis is the result of this bacterial and host inflammatory reactions the treatments are directed controlling both of them and improving the inherent healing capacity of the tissue wherein platelets also play a role by integrating complex cascades between their mediators (16,17)

The most commonly followed surgical treatment protocol for periodontitis is flap surgery. Periodontal flap surgeries are done to prevent or correct anatomical, developmental, traumatic or plaque induced defects of the gingiva, bone and alveolar mucosa. Pockets on the teeth, in which a complete removal of root irritants is not clinically possible, goes for a periodontal surgery. (18) Gottlieb stated, “presence of pocket is a chief prerequisite for the existence of pyorrhea, with bacterial activity and inflammation.” Flap surgeries can be done to access to root defects, resective surgery, regenerative surgery, periodontal flap surgery (esthetic crown lengthening, papilla reconstruction, gingival enlargement, biopsy, pre prosthetic surgeries such as crown lengthening, gingival and ridge augmentation and vestibuloplasty.) Flap surgeries cannot be done in patients with uncontrolled medical conditions, poor plaque control, high caries risk and unrealistic patient desires.

Chronic periodontitis may warrant periodontal surgery procedures. Out of the various factors, the most common and important aspect is prevention of infection. Sources of infection may include instruments, hands of surgeon, air of operative, patient’s nose, perioral skin and saliva. Therefore, preventive measures can be taken care such as disinfection, proper sterilisation, and barrier techniques. If such measures are taken, there is a very low rate of postoperative infection post surgery, thereby, eliminating the use of antibiotics as a prophylactic measure.^(19,20) In India, the dentists have been known to prescribe antibiotics more than any other medical personnel, which is totally based on observations, without any protocol. Indiscriminate use of antibiotics carry the risk of development of gastrointestinal problem, colonisation of resistant or fungal strains, cross relations with other drugs, allergies and increased cost of the treatment. (21,22)

A complication is defined as a secondary disease developing in the course of the primary disease. The most common complication seen post periodontal surgery is post operative pain, bleeding, root hypersensitivity, delayed healing, taste changes, which is known to alter the periodontal outcome (23). Usage of antibiotics post surgery for reducing the postoperative complications and enhancing healing is debatable. It has been reported that the postoperative complications after periodontal flap surgery were very less (1.87- 3.25%) and there was no significant difference between the groups with or without antibiotics (24). At the same time it has also been reported that adjunctive use of antibiotics improved the clinical parameters after flap surgery. (25) Our team has extensive knowledge and research experience that has translate into high quality publications (Neelakantan *et al.*, 2011; Felicita, Chandrasekar and Shanthasundari, 2012; Jain, Kumar and Manjula, 2014; Kamisetty *et al.*, 2015; Lakshmi *et al.*, 2015; Keerthana and Thenmozhi, 2016; Mootha *et al.*, 2016; Kumar, 2017; Azeem and Sureshbabu, 2018; Chen *et al.*, 2019)

The aim of the study was to evaluate whether antibiotics are prescribed or not to patients undergoing flap surgery, the choice of antibiotics prescribed and its influence on postoperative healing and postoperative complications.

MATERIALS AND METHOD:

Study setting:

The present hospital based retrospective study was carried out with the use of electronic case records of 701 patients who underwent flap surgery from all the patients attending a dental hospital from June 2019 to March 2020. Ethical clearance was obtained from the Institutional Board Committee - SDC/SIHEC/2020/DIASDATA/0619-0320. Population sample was 701 patients. The number of people involved were 2 examiners (One PI, One guide).

Sampling:

After assessment of the patient data, case records of 701 patients who underwent flap surgery were included in the study. Consecutive sampling method was carried out. Cross verification of data was done via photographs, data evaluation was done with two reviewers and cross verified with third reviewer. Inclusion criteria included patients undergoing flap surgery for the treatment of periodontitis, systemically healthy patients. Exclusion criteria included patients with incomplete case records and case records which are not approved by the specialists.

Data collection and tabulation:

All preoperative, Intra operative, immediate postoperative and one week postoperative records were retrieved. The variables collected include the age of the patient, gender of the patient, the site of the surgical site, the details regarding the antibiotics prescribed, one-week postoperative healing and the postoperative complications. The healing index was assessed from the digital photographs taken one week postoperatively by a single calibrated examiner. Postoperative healing was graded based on the healing index on a scale 1-5 as described by Landry, Turnbull and Howle^(Pippi, 2017) (1- very poor, 2 - poor, 3-good, 4 - very good, 5 - excellent).

Statistical analysis:

Statistical analysis was done using Statistical Package for Social Sciences for Windows, Version 20.0 (SPSS Inc., Chicago, IL USA). Descriptive statistics was done using percentage for qualitative data and mean and standard deviation for quantitative data. Gender and site of surgery were considered as independent variables and antibiotics prescribed as the dependent variable to evaluate the influence of gender or site of surgery on antibiotic prescription. Whereas to evaluate the influence of antibiotics on postoperative healing and complications the antibiotics were considered as the independent variable and healing index and postoperative complications as the dependent variable. Chi square test was performed to assess the association between the gender and antibiotics prescribed to the patients, Site of surgery and the antibiotics prescribed and the postoperative complications and the antibiotics prescribed. One way Anova test was done to compare the postoperative healing (quantitative score) between flap surgeries done with or without various antibiotics. The p-value <0.05, was considered as statistically significant.

RESULTS:

A total of 701 patients with 58% males and 42% females with age range of 18-65 years old were involved in the study. Out of 701 patients, 656 patients were prescribed antibiotics while the other 45 patients (6.42%) were not prescribed any antibiotics postoperatively after periodontal flap surgery. Among the antibiotics prescribed the most common was amoxicillin (57.34%) followed by amoxicillin along with metronidazole (22.84%). Amoxicillin with clavulanic acid also was used in 13.12% of cases. The drugs like Azithromycin and doxycycline were rarely used.

The most commonly prescribed antibiotics were Amoxicillin (55.64% for males and 59.73% for females) followed by Amox+Metronidazole (22.55% for males and 23.21% for females). There was no statistically significant difference in the antibiotics usage between males and females. ($p>0.05$) as shown in Figure 1 and Table 1.

Results of the study show that overall upper quadrants(Q1 and Q2) had more flap surgeries than lower quadrants. While comparing the surgeries done sextant wise, sextant 3 was the most operated site as compared to other sextants. Out of the antibiotics such as Amoxicillin, Amoxicillin+Metronidazole, Amoxicillin+Clavulanic acid, Azithromycin and Doxycycline, the most preferred antibiotic prescribed was Amoxicillin (n=407) followed by Amoxicillin+Metronidazole (n=160). In this study, it was seen that there was no significant relationship between the site of the surgery and the antibiotics prescribed. ($p>0.05$) as seen in Figure 2 and Table 2.

The comparison of the postoperative healing with the antibiotics prescribed was done using Anova test and found that there was no significant difference in the healing index with or without antibiotic usage and also between the different antibiotics ($p>0.05$) as seen in Figure 3 and Table 3. In all the groups mean healing index was slightly less than 4. The two antibiotics which were rarely used (Doxycycline and Azithromycin) were not included in the statistical analysis as the number of patients in those groups were very few (only one case for each drug)

The postoperative complications were evaluated and compared in this study. Reported complications were very less (1.24%). In the group which didn't take antibiotics, the reported complications were 3.5% whereas in the group with antibiotics showed 1.07%. The reported postoperative complication in the present study was ulcer formation, which was seen in the patients who were prescribed Amoxicillin (n=2). Even though there was a slight variation in the postoperative complication with and without antibiotics and between different antibiotics the difference was not statistically significant. ($p>0.05$) seen in Figure 4 and Table 4.

DISCUSSION:

From the study, it can be interpreted that for the majority of patients (93.58%) antibiotics were prescribed postoperatively after periodontal flap surgeries whereas only 6.42% no antibiotics were prescribed post surgically. A systematic review including eighty three trials has reported that antibiotics were used in 75.4% of flaps. (Liu *et al.*, 2017) Comparing these results the present results shows much higher usage of antibiotics. Out of all the antibiotics prescribed, the most commonly prescribed was Amoxicillin group and Amoxicillin+Metronidazole group. The least prescribed antibiotic was Doxycycline. Similar findings were reported by Dibart *et. al* (Dibart, 2020) and Ross *et. al* (29). They reported that Amoxicillin and Doxycycline were chosen mainly because of its effect against periodontal pathogens and due to convenience of its usage, which thereby improves patient compliance. At the same time Metronidazole was not considered, as patient compliance has been found to be poor due to its side effects. (30)

The present study reveals that there is no significant difference in the healing index between flap surgeries done with or without postoperative antibiotics. Supporting the results of the present study it has been reported that antibiotic usage did not influence the outcome of periodontal flap surgery wherein they have compared healing after flap surgery with and without antibiotics. (31) The results of the study also reveals that there was no significant difference between the flap surgeries done with different antibiotics. This questions the usefulness of antibiotics in postoperative management and suggests that for flap surgeries the postoperative antibiotics usage can be reduced. Present study included all types of flap surgeries in which a few cases were with osseous surgeries including bone grafting and guided tissue regeneration. But since separate analysis was not done to analyse the usefulness of antibiotics in such situations no conclusion can be derived on the same

On gender wise comparison; it was found that males underwent more flap surgery than females. This is in accordance with many studies that males have more periodontal disease than females. (Shiau and Reynolds, 2010) On antibiotic prescription females were prescribed comparatively more antibiotics (94.53%) than males (92.89%). Supporting our results studies done by Weibke *et.al* (Schröder *et al.*, 2016) and David *et.al*, (Smith *et al.*, 2018) reported that females were more commonly prescribed antibiotics than males as gender differences in bacterial infections might be related to genetic background.

According to our study, there was no significant difference between the site of surgery with the antibiotics prescribed. Mehta et. al (Mehta, 2020) and Desye et.al, (Misganaw, Linger and Abesha, 2020) reported similar results that there was no association between the site of surgery and the antibiotics prescribed.

While analysing the postoperative complication in the majority of cases there were no postoperative complications reported. In the group which didn't take antibiotics, the reported complications were 3.5% whereas in the group with antibiotics showed 1.07%. Even though the percentage was slightly more in group without antibiotic usage the difference was not statistically significant. Similarly, it has been reported that surgeries which used antibiotics had Lower complications (0.073%) than the surgeries done without the antibiotics (0.693%). Ulcer was the only postoperative complication found in a very few cases of the present study. Studies by Pendrill et. al (Pendrill and Reddy, 1980) and Porwal et.al, (Porwal *et al.*, 2019) reported that the most common complications were ulceration or necrosis, signs of delayed healing, adverse systemic effects such as fever, malaise, lassitude, etc indicated that there was no difference between any of the groups.

This study being a retrospective study had inherent limitations. The healing was evaluated only at one week postoperatively and no long term evaluation was done. The factors such as patients compliance for medication, oral hygiene maintenance and the type of surgical techniques which might have an influence on healing were not included in the analysis. Larger sample size is one of major strengths of the study and to a certain extent it can minimise these limitations. Within the limits the results of the study clearly expose the fact that antibiotics are very commonly used in periodontal surgeries even though it is not making much difference in improving healing or reducing postoperative complications. Further controlled studies are needed to prove these facts.

CONCLUSION:

Within the limits of the study, it can be concluded that antibiotics are frequently prescribed postoperatively after flap surgeries and the most commonly prescribed antibiotic was Amoxicillin followed by Amoxicillin+Metronidazole. Gender or site of surgery are not having any influence on antibiotic prescription. There is no significant difference in the postoperative healing or postoperative complications between flap surgeries done without antibiotics or with different types of antibiotics.

CLINICAL SIGNIFICANCE: This study reports the uselessness of postoperative antibiotic usage after periodontal flap surgery.

AUTHORS CONTRIBUTIONS:

First author (Palak Mayur Shah) performed the analysis, and interpretation and wrote the manuscript. Second author (Dr. Sheeja Varghese) contributed to conception, data design, analysis, interpretation and critically revised the manuscript. Third author (Dr. Manjari Chaudhary) participated in the study and revised the manuscript. All the three authors have discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST: No conflict of interest.

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FIGURE AND LEGENDS:

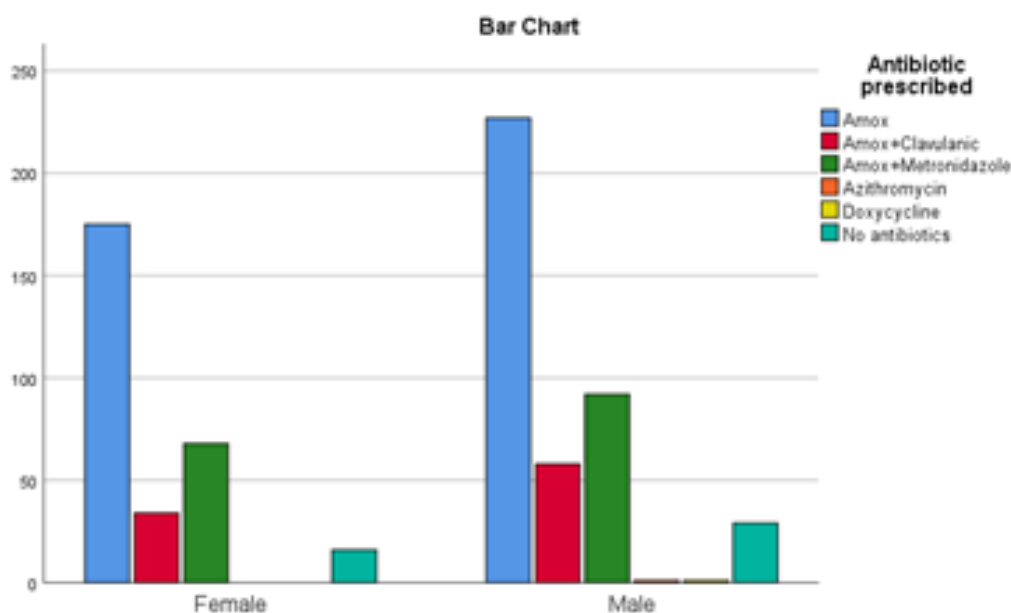


Figure 1: The bar graph showing the distribution of post surgical antibiotics usage between males and females. The X axis represents the gender distribution and Y axis represents the number of patients who were prescribed the respective antibiotics. Blue denotes Amoxicillin, Red - Amox+Clavulanic acid, Green - Amox+Metronidazole, Orange- Azithromycin, Yellow-Doxycycline, Light blue - No antibiotics. Overall males underwent more flap surgery

than females but there is no significant difference in antibiotics usage between males and females. Chi-square test: $p > 0.05$ - Statistically insignificant)

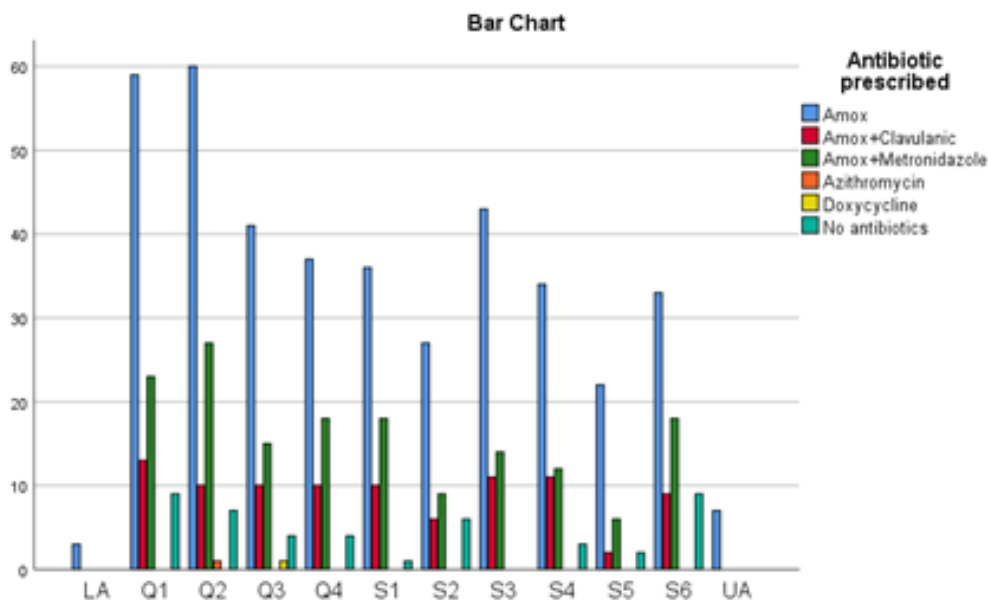


Figure 2: The bar chart showing the distribution of antibiotics prescription with respect to the site of surgery. The X axis represents the site of surgery and Y axis represents the number of patients where the respective antibiotics is prescribed. Blue denotes Amoxicillin, Red - Amox+Clavulanic acid, Green - Amox+Metronidazole, Orange-Azithromycin, Yellow-Doxycycline, Light blue - No antibiotics. (Q -quadrants, S- for sextants, UA- upper arch, LA- Lower arch). Overall maxillary arch has more surgeries than the mandibular arch. The most common antibiotic prescribed was amoxicillin followed by Amoxicillin + clavulanic acid. But there is no significant difference between sites with respect to antibiotics prescribed. (Chi-square test: $p > 0.05$)

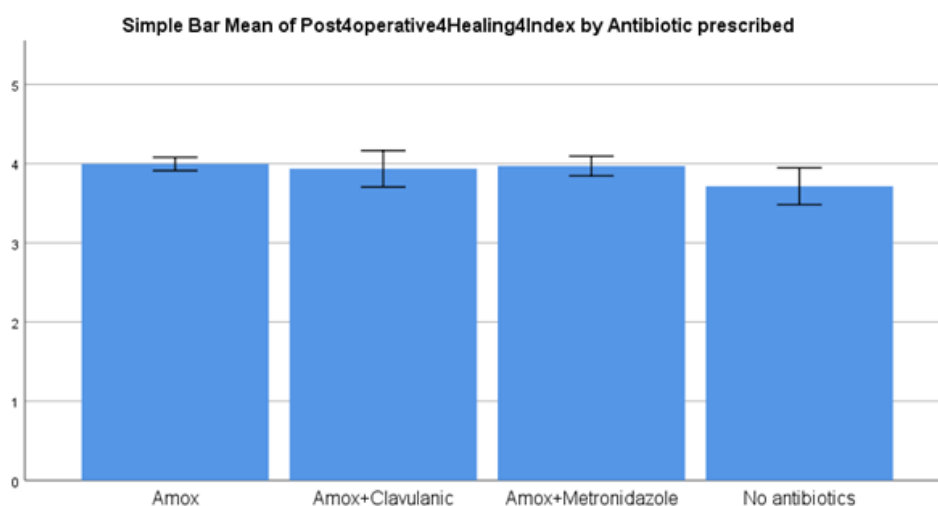


Figure 3: The bar graph with error bar showing the comparison of postoperative healing index between flap surgeries with different antibiotics and without antibiotics. The X axis represents the groups with different antibiotics prescribed and Y axis represents the mean postoperative healing index. There was no significant difference in the healing index between the groups with antibiotic and without antibiotics as well as between different antibiotics.

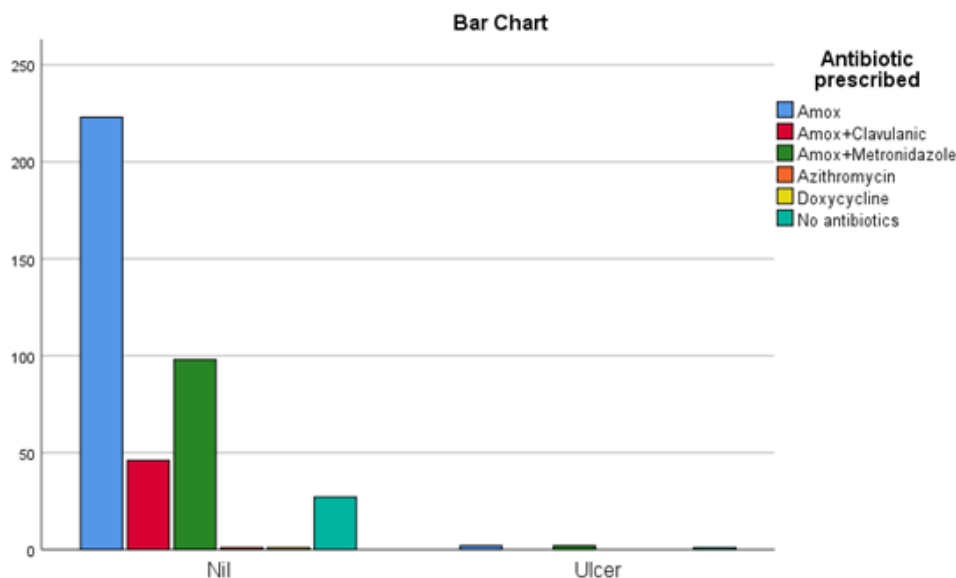


Figure 4: The bar chart showing the distribution of postoperative complications based on the antibiotics prescribed. The X axis represents postoperative complication/ outcome (Nil indicates no complication) and Y axis represents the number of patients with the respective outcome between different antibiotics. . Blue denotes Amoxicillin, Red - Amox+Clavulanic acid, Green - Amox+Metronidazole, Orange- Azithromycin, Yellow-Doxycycline,Light blue - No antibiotics. There is no significant difference in the postoperative complication between different antibiotics prescribed. (Chi-square test: $p>0.05$)

TABLE AND LEGENDS:

Table 1: The table showing the distribution of the antibiotics prescription between genders. The most prescribed antibiotic is Amoxicillin (57.34%), followed by amoxicillin +Metronidazole (22.82%). Antibiotics are not prescribed for 6.42% of patients. There is no significant difference between genders with respect to antibiotic usage. Statistical comparison of antibiotic usage between males and females using chi square test : There is no significant difference between genders with respect to antibiotics prescribed. (Chi-square test: $p>0.05$ - Statistically insignificant)

Antibiotics	Amox	Amox+Metronidazole	Amox+Clavulanic acid	Azithromycin	Doxycycline	No antibiotics	Total	Chi-square test		
								Pearson chi-square value	df	p-value
Male N (%)	227 (55.64%)	92 (22.55%)	58 (14.22%)	1 (0.25%)	1 (0.25%)	29 (7.11%)	408 (100.00%)	3.573	5	0.524
Female N (%)	175 (59.73%)	68 (23.21%)	34 (11.60%)	0 (0.00%)	0 (0.00%)	16 (5.46%)	293 (100.00%)			
Total N (%)	402	160 (22.82%)	92	1	1	45	701			

(57.34)	(13.12%)	(0.14%)	(0.14 %)	(6.42 %)	(100. 00%)			
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Table 2: The table showing the distribution of the antibiotics prescription based on the site of surgery. LA indicates lower arch. UA indicates upper arch Q indicates quadrant and S indicates sextant. The most commonly operated site was Quadrant 2 and the most prescribed drug was Amoxicillin followed by Amox+Metronidazole. There is no significant difference between the site of surgery with respect to the antibiotics prescription. There is no significant relationship between the site of surgery and antibiotics prescribed. (Chi-square test: $p > 0.05$ - Statistically insignificant)

Site of surgery	Amox N(%)	Amox+ Metronidazole N(%)	Amox+ Clavulanic N(%)	Azithromycin N(%)	Doxycycline N(%)	No antibiotics N(%)	Total	Chi-square test		
LA	3 (0.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3	Pearson's Chi-square value 46.913	df 55	P-value 0.773
Q1	59 (14.68%)	23 (14.38%)	13 (30.23%)	0 (0.00%)	0 (0.00%)	9 (28.0%)	104			
Q2	56 (14.93%)	27 (16.88%)	10 (2.49%)	1 (100.00%)	0 (0.00%)	7 (25.5%)	101			
Q3	41 (10.20%)	15 (9.38%)	10 (2.49%)	0 (0.00%)	1 (100.00%)	4 (20.8%)	71			
Q4	37 (9.20%)	18 (11.25%)	10 (2.49%)	0 (0.00%)	0 (0.00%)	4 (20.8%)	69			
S1	36 (8.96%)	18 (11.25%)	10 (2.49%)	0 (0.00%)	0 (0.00%)	1 (12.2%)	65			
S2	27 (6.72%)	9 (5.63%)	6 (1.49%)	0 (0.00%)	0 (0.00%)	6 (13.3%)	48			
S3	43 (10.70%)	14 (8.75%)	11 (20.74%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	68			

S4	34 (8.46%)	12 (7.50%)	11 (20.74%)	0 (0.00%)	0 (0.00%)	3 (6.66%)	
S5	22 (5.47%)	6 (3.75%)	2 (10.50%)	0 (0.00%)	0 (0.00%)	2 (4.44%)	32
S6	34 (8.21%)	18 (11.25%)	9 (2.24%)	0 (0.00%)	0 (0.00%)	9 (20.0%)	70
UA	7 (1.74%)		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7
		0 (0.00%)					
Total	402 (100%)	160 (100.00%)	92 (100.00%)	1 (100.00%)	1 (100.00%)	45 (100.00%)	701

Table 3: Comparison of mean healing index between flap surgeries done with or without antibiotics. There is no significant difference in the healing index between flap surgeries done with or without different antibiotics. (Anova test: $p > 0.05$ - Statistically not significant)

Bayesian Estimates of Coefficients^{a,,b,c}

Parameter	Posterior		95% Credible Interval	
	Mean	Variance	Lower Bound	Upper Bound
Antibiotic prescribed = Amox	3.995	0.002	3.91	4.081
Antibiotic prescribed = Amox+Clavulanic	3.935	0.009	3.748	4.122
Antibiotic prescribed = Amox+Metronidazole	3.97	0.004	3.843	4.097
Antibiotic prescribed = Azithromycin	3	0.419	1.731	4.269
Antibiotic prescribed = Doxycycline	4	0.419	2.731	5.269
Antibiotic prescribed = No antibiotics	3.714	0.015	3.475	3.954

a. Dependent Variable: Postoperative healing index						
b. Model: Antibiotic prescribed						
c. Assume standard reference priors.						
ANOVA						
Post operative healing index	Sum of Squares	df	Mean Square	F	Sig.	Bayes Factor ^a
Between Groups	2.929	5	0.586	1.407	0.221	0
Within Groups	162.424	390	0.416			
Total	165.354	395				

Table 4: The table showing the distribution of the postoperative complication after flap surgery based on the antibiotics prescribed. Majority of cases showed no complications. The postoperative complication reported was ulcer in 2 patients who took Amoxicillin, 2 patients who took Amoxicillin +Metronidazole and 1 patient with no antibiotics. There is no significant difference in the postoperative complications between patients with or without antibiotics after flap surgery. (Chi-square test: $p > 0.05$ - Statistically insignificant)

Postoperative complications	Amox N(%)	Amox+ Clavulanic N(%)	Amox+ Metronidazole N(%)	Azithromycin N(%)	Doxycycline N(%)	No antibiotics N(%)	Total N(%)	Chi-square test		
								Pearson's chi-square value	df	P-value
Nil	223 (99.1%)	46 (100%)	98(98%)	1(100%)	1 (100%)	27 (96.4%)	396 (98.75%)	2.53	8	0.772
Ulcer	2 (0.9%)	0 (0%)	2 (2%)	0(0.00%)	0 (0.00%)	1 (3.5%)	5 (1.24%)			
Total	225 (100%)	46 (100%)	100 (100%)	1 (100%)	1 (100%)	28 (100%)	401 (100%)			