

ORIGINAL RESEARCH

Effect Of Uninterrupted Antiplatelet Therapy On Postextraction Bleeding Following Single Dental Extraction: An Original Research

¹Dr. George Skariah P, ²Dr. Sherin Shahana

¹Associate Professor Department of Oral and Maxillofacial Surgery, Govt. Dental College, Trivandrum, Kerala, India

²Consultant, Oral and Maxillofacial Surgeon, Al Nahda, Dubai, UAE

Corresponding author

Dr. George Skariah P

Associate Professor Department of Oral and Maxillofacial Surgery, Govt. Dental College, Trivandrum, Kerala, India

Email: georgeclt@gmail.com

Received: 18 October, 2022

Accepted: 21 November, 2022

ABSTRACT

Background: Cardiovascular diseases is considered to be the most common cause of death in the Western world and its treatment frequently requires therapy with antiplatelet agents, which increases the haemorrhage risk after oral surgical procedures. There exists a controversy between the continuation of the antiplatelet agents for the fear of cardiac events and the stoppage of the medications for the fear of post operative bleeding. The aim of this study is to evaluate the post extraction bleeding after single dental extraction, among patients on uninterrupted single or dual antiplatelet therapy and compare with healthy controls.

Objectives: To assess and compare the immediate (30 minutes after extraction) and late (60 minutes) post extraction bleeding following single dental extraction among healthy patients and patients on uninterrupted aspirin(75mg)/ clopidogrel(75mg)/ aspirin(75mg) + clopidogrel(75mg).

Methods: A total of n=100 study subjects were considered for study of which 50 patients on uninterrupted antiplatelet therapy, either aspirin or clopidogrel or both, requiring dental extraction were considered to be as the case group and 50 healthy patients requiring dental extraction were grouped as the control group. Extraction of the indicated tooth was done in both case and control group by the same operator. All the patients were observed for bleeding after 30 minutes and 60 minutes post extraction.

Results: In the case group, majority of the patients were in the age group of 61-70years (56%) and 51-60 years (38%) in the control group. The prevalence of anti platelet therapy usage was more among the males in comparison to females. Majority of the patients reported for extraction of tooth due to unrestorable caries in both the groups (76% in case and 74% in control group), followed by extraction due to periodontal problems. 66% of the patients were under single antiplatelet therapy with aspirin, followed by 24% of patients under dual antiplatelet therapy with aspirin and clopidogrel and 10% under single antiplatelet therapy with clopidogrel. The main reason for antiplatelet therapy was found to be coronary artery disease (90%), followed by CVA (6%) and PAD (4%). Only 4% of patients in the case group had bleeding

30minutes post extraction, which was managed by local haemostatic measure, and there was no bleeding noted 60 minutes post extraction in both case and control group.

Interpretation and conclusion: Interruption of antiplatelet therapy prior to single dental extraction is not necessary, and there is no hemorrhagic risk associated with it. Local haemostatic measures are sufficient to control bleeding.

Key Words: Antiplatelet, Bleeding, Dental Extraction.

INTRODUCTION

Cardiovascular diseases cause the highest mortality and morbidity worldwide. With increasing awareness, health consciousness and preventive strategies, there is a striking decrease in cardiovascular mortality, resulting in fewer deaths compared with the earlier decades. The introduction of preventive and maintenance antiplatelet therapy has to a certain extent contributed to this decline. Antiplatelet therapy has been reported to have reduced the overall mortality of vascular diseases by 15% and nonfatal vascular complications by 30%(1). Antiplatelet therapies have become the cornerstone of clinical management of acute coronary syndrome (ACS). The development of percutaneous coronary intervention (PCI) is considered to be the driving force behind the evolution of antiplatelet regimen as prevention for early stent thrombosis. Anti platelet or platelet aggregation inhibitor drugs can reversibly or irreversibly inhibit the platelet activation resulting in decreased tendency of platelets to adhere to one another and to damaged blood vessels endothelium. Antiplatelet agents are used in the primary and secondary prevention of cardiac and cerebrovascular diseases, specifically for the prevention of arterial and venous thrombosis in patients with conditions such as ischemic heart disease, prosthetic heart valves, and coronary artery stents and those at risk for ischemic cerebrovascular accidents. The different classes of antiplatelet drugs include irreversible cyclooxygenase inhibitors (aspirin), ADP receptor inhibitors (clopidogrel, prasugrel), phosphodiesterase inhibitors (cilostazol), protease – activated receptor 1 antagonists, glycoprotein IIB/IIA inhibitors (abciximab), adenosine reuptake inhibitors (dipyridamole), and thromboxane inhibitors. Low doses of aspirin, clopidogrel, ticlopidine, ticagrilor and dipyridamole are the most commonly used antiplatelet drugs. Aspirin, irreversibly inactivates the enzyme cyclooxygenase and thereby prevents synthesis of thromboxane A₂, which has an important role in platelet aggregation. Aspirin affects the activity of platelets during their lifetime (7-10 days). Clopidogrel, ticlopidine, and prasugrel (thienopyridines) inhibit adenosine- diphosphate (ADP) receptors within 2hrs and last for 7-10 days of the mean platelet life. Dual therapies have synergistic antiplatelet effects, as the two drugs affect platelet aggregation by different mechanisms. The combination of low-dose aspirin and clopidogrel is mainly used to prevent thrombotic complications after percutaneous insertion of coronary stents. Compared with aspirin alone, dual oral antiplatelet therapy can provide an additional 20% reduction in relative risk of myocardial infarction and stroke. They are associated with greater antithrombotic effect, but also with a higher bleeding risk than aspirin.(2) When patients under such antiplatelet therapy require surgery, the surgeon is confronted with the choice of either interrupting the antiplatelet therapy, which increases the risks of thrombosis, or continuing the medication, which on the other hand increases the risk of hemorrhage. Published studies commonly recommended continuation of antiplatelet drugs for minor oral surgical procedures. Most western studies have reported that single antiplatelet therapy should not be stopped prior to dental surgical procedures and that patients on dual antiplatelet therapy may need to be referred to a hospital based dental clinic. Nevertheless, there is a lack of published evidence about peri-operative dental management of the patients on dual and non-aspirin antiplatelet drugs. This study tries to evaluate and compare the post extraction bleeding after single dental extraction, among patients on uninterrupted single or dual antiplatelet therapy with healthy controls.

AIMS AND OBJECTIVES

To evaluate the post extraction bleeding after single dental extraction, among patients on uninterrupted single or dual antiplatelet therapy and compare with healthy controls. To assess and compare the immediate (30 minutes after extraction) and late (60 minutes) post extraction bleeding following single dental extraction among healthy patients and patients on uninterrupted aspirin(75mg)/ clopidogrel(75mg)/ aspirin(75mg)+clopidogrel(75mg).

MATERIALS AND METHODS

Study Design is Observational analytical study. Study Setting is in Department of oral and maxillofacial surgery, Government Dental College, Thiruvananthapuram. Every patient who reported to OPD of Oral and Maxillofacial Surgery-Government Dental College, Thiruvananthapuram, satisfying the research criteria in the study period was included in the study. Inclusion: Patients on single or dual antiplatelet therapy, and are in need of single dental extraction. Patients on antiplatelet therapy, with the dosage of aspirin-75mg and/or clopidogrel- 75mg. Patients in the age group of 18yrs -65yrs.

EXCLUSION

Patients with liver disease, bleeding or clotting disorders and on immunosuppressive therapy. Patients reporting for extraction of impacted tooth. Patients who had stopped the single or both antiplatelet drugs before extraction. Study Population: Healthy patients and patients on uninterrupted antiplatelet, who reported in the OPD of Oral and Maxillofacial Surgery, Government Dental College, Trivandrum for single dental extraction.

CLINICAL ASSESSMENT

Variables- Age, Gender, Indication for extraction, Type of antiplatelet therapy, Reason for antiplatelet therapy, Post extraction bleeding- 30 minutes and 60 minutes

SAMPLE SIZE

The sample size was n=100 in which 50 patients were included in both study and control groups. Thiruvananthapuram, satisfying the research criteria in the study period was included in the study. A total of 50 patients were studied in each group. Based on gender,35 patients (70%) were male and 15 patients (30%) were female, whereas in the control group, 20 patients (40%) were male and 30 patients (60%) were female. Based on age, Majority of the patients were in 61-70years (56%) in the case group, whereas majority of the patients were in the age group of 51-60 years (38%) in the control group.

STATISTICAL METHODS

Sample size, $n = 2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 \frac{P_1 - P_0}{P_1 P_0}$, Where, n = Sample size, $Z_{1-\alpha/2} = 1.96$ and $Z_{1-\beta} = 0.84$ - constant. P_1 = proportion of patients on antiplatelet therapy with immediate bleeding (2.4) P_0 = proportion of patients in control group with immediate bleeding (0.4). So, $n = 2 \times 7.9 \times 2.4 \times 0.976 = 2 \times 4.62 = 9 (2.4 - 0.4)^2$. The minimum sample size required for each group was calculated as 9 The minimum sample size required in total was 18. The sample size for each group in my study was taken as 50. [Theodoros Lillis, Antonios Ziakas, Konstantinos Koskinas, Anastasios Tsirlis, George Giannoglou: Safety of dental extractions during uninterrupted single or dual antiplatelet treatment (Am J Cardiol 2011; 108:964-967)]

RESULTS

Every patient who reported to OPD of Oral and Maxillofacial Surgery-Government Dental College

Descriptive data Age: The age of patients in both the groups ranged from 37 to 65 years.

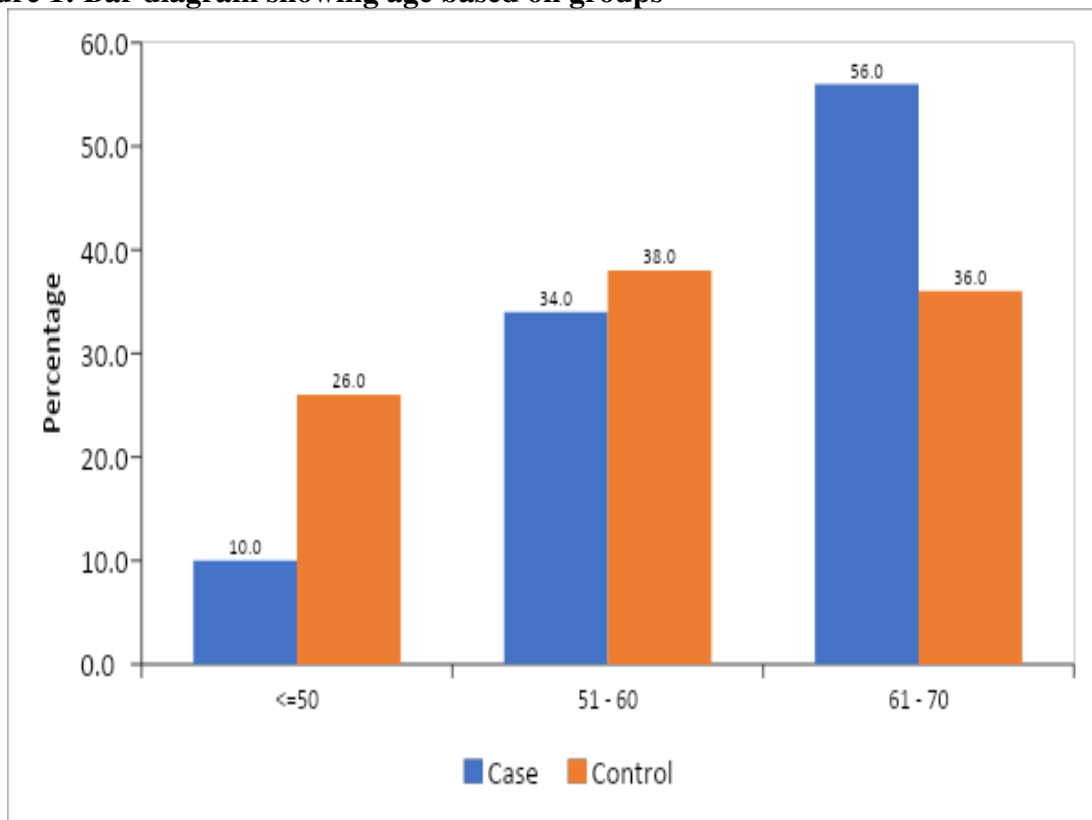
The mean age in the group with patients on anti platelet therapy was 60.2 ± 6.5 and those patients without any antiplatelet therapy were 56.3 ± 8 . Majority of the patients were in 61-70years (56%) in the case group, whereas majority of the patients were in the age group of 51-60 years (38%) in the control group. (see table1 and figure 1)

Table 1: Comparison of age based on groups

Age	Case		Control	
	Count	Percent	Count	Percent
<=50	5	10.0	13	26.0
51 - 60	17	34.0	19	38.0
61 - 70	28	56.0	18	36.0
Mean \pm SD	60.2 \pm 6.5		56.3 \pm 8	

t = 2.68**, p = 0.009

Figure 1: Bar diagram showing age based on groups



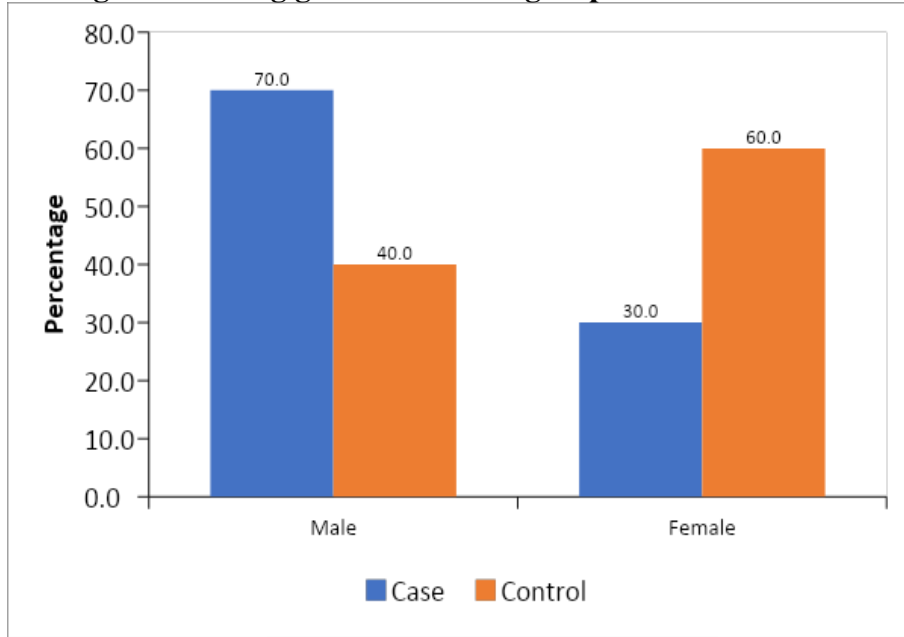
Gender: Among 50 patients in the case group, 35 patients (70%) were male and 15 patients (30%) were female, whereas in the control group, 20 patients (40%) were male and 30 patients (60%) were female. Prevalence of anti platelet therapy was more among males.(see table 1 figure 2)

Table 2: Comparison of gender based on groups

Gender	Case		Control		χ^2	p
	Count	Percent	Count	Percent		
Male	35	70.0	20	40.0	9.09**	0.003
Female	15	30.0	30	60.0		

**:- Significant at 0.01 level

Figure 2: Bar diagram showing gender based on groups

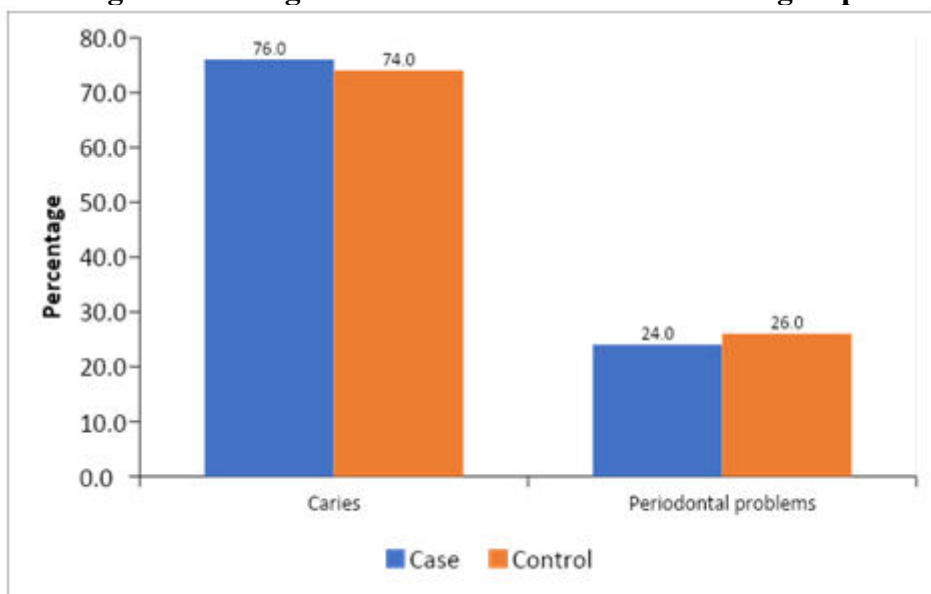


Indication for extraction: Majority of the patients reported for extraction due to non-restorable caries of teeth in both the groups, 76% in case group and 74% in control group. Remaining patients reported due to periodontal problems, 24% in case group and 26% in control group. There was no significant relationship between anti platelet therapy and indication for extraction ($p = 0.817$) (see table 3 and figure 3)

Table 3: Comparison of indication for extraction based on groups

Indication for extraction	Case		Control		χ^2	p
	Count	Percent	Count	Percent		
Caries	38	76.0	37	74.0	0.05	0.817
Periodontal problems	12	24.0	13	26.0		

Figure 3: Bar diagram showing indication for extraction based on groups

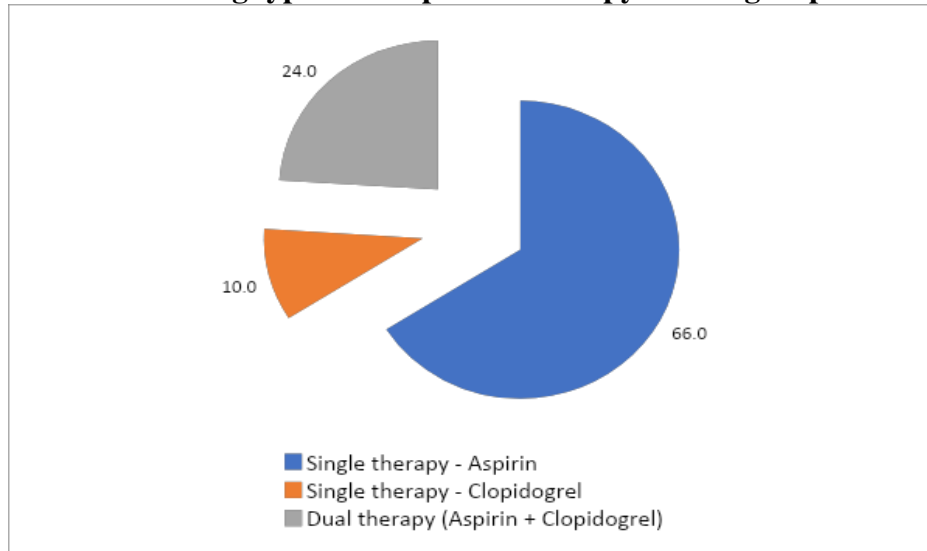


Type of anti platelet therapy: 66% of the patients in the case group were under single anti platelet therapy with aspirin, 24% of patients on dual anti platelet therapy and 10% of patients under single anti platelet therapy with clopidogrel.(see table 4 and figure 4)

Table 4: Percentage distribution of the sample according to type of anti platelet therapy in case group

Type of anti platelet therapy	Count	Percent
Single therapy - Aspirin	33	66.0
Single therapy - Clopidogrel	5	10.0
Dual therapy (Aspirin + Clopidogrel)	12	24.0

Figure 4: Pie chart showing type of anti-platelet therapy in case group

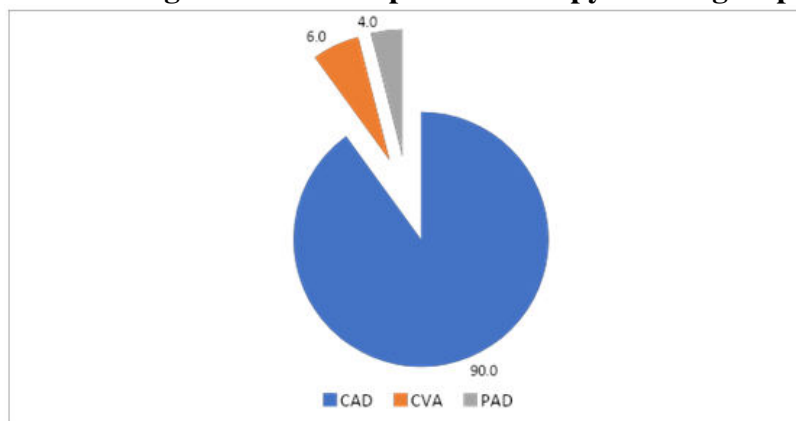


Reason for anti-platelet therapy: Majority of the patients (90%) were under anti-platelet therapy due to coronary artery disease (CAD), whereas only 6% presented with cerebrovascular accident and 4% with peripheral arterial disease. (see table 5 and figure 5)

Table 5: Percentage distribution of the sample according to reason for anti platelet therapy in case group

Reason for anti platelet therapy	Count	Percent
CAD	45	90.0
CVA	3	6.0
PAD	2	4.0

Figure 5: Pie chart showing reason for antiplatelet therapy in case group



Outcome data & Main Results: On evaluation of bleeding after 30 minutes of post extraction period, bleeding was noticed in 2 patients under anti platelet therapy, which was managed by applying a pressure pack for 30 minutes further. 96% of the patients did not encounter any bleeding episodes and also there was no bleeding noticed in any of the control group patients. No significant relationship was found between bleeding and antiplatelet therapy ($p = 0.153$). (see table 6,7 and figure 6,7) There was absolutely no bleeding noted in any of the patients in both case and control group, after 60minutes of extraction. Hemostasis was achieved for the 2 patients who had bleeding, 30minutes post extraction in the case group.

Table 6: Comparison of bleeding between groups at 30 minute after extraction

Bleeding at 30 minute	Case		Control		χ^2	p
	Count	Percent	Count	Percent		
Absent	48	96.0	50	100.0	2.04	0.153
Present	2	4.0	0	0.0		

Figure 6: Bar diagram showing bleeding between groups at 30 minute after extraction

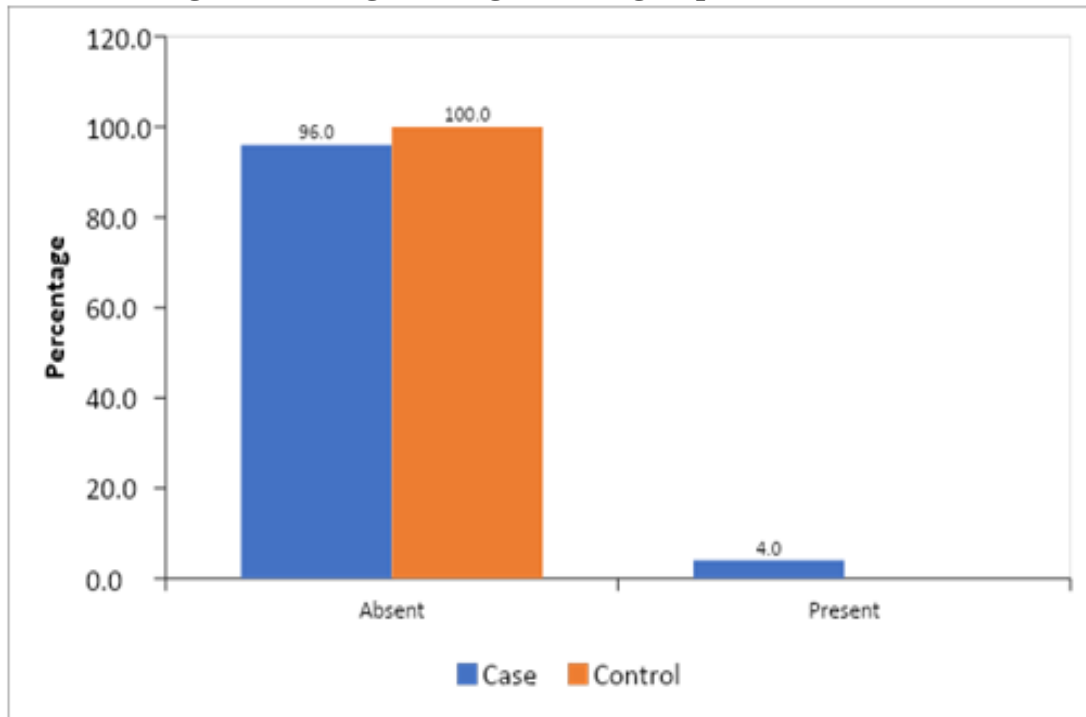
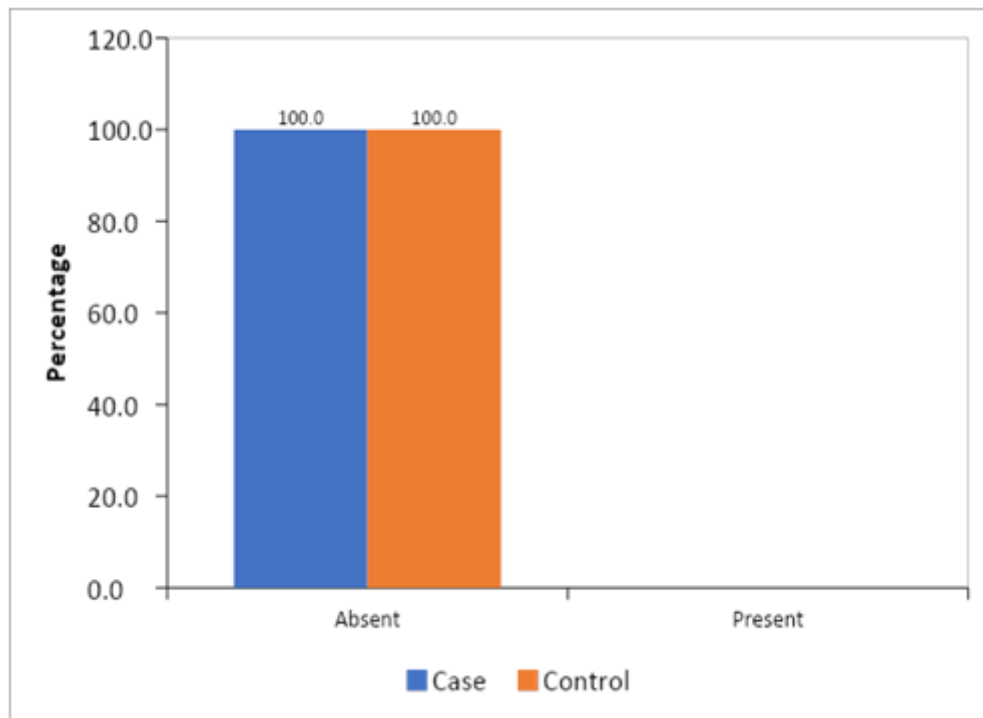


Table 7: Comparison of bleeding between groups at 60 minute after extraction

Bleeding at 60 minute	Case		Control		χ^2	p
	Count	Percent	Count	Percent		
Absent	50	100.0	50	100.0	-	-
Present	0	0.0	0	0.0		

Figure 7: Bar diagram showing bleeding between groups at 60 minute after extraction

DISCUSSION

Adequate hemostasis is required post any invasive dental treatment, because uncontrollable bleeding can lead to many serious complications. Cardiovascular disease is considered to be the most common cause of death by various studies in the present era. In 2005, cardiovascular disease was the underlying cause of death in 864,480 of the approximately 2.5 million total deaths in the US, and the adults aged >65 years accounted for 82 % of deaths. (3)A significant percentage of the population is under anti-platelet therapy for the treatment and prevention of thromboembolic diseases such as myocardial infarction, ischemic stroke, cerebrovascular accidents and peripheral arterial disease. Patients with coronary artery stents are also under antiplatelet therapy and their premature discontinuation can lead to stent thrombosis. The incidence of stent thrombosis was found to be 64.4% in the 1990's, with the mortality rate ranging from 20-45%. In the current era with the usage of dual antiplatelet therapy, the occurrence of subacute stent thrombosis has been found to be 1%. (4) Aspirin and/or clopidogrel are the most commonly used antiplatelet drugs in India. It was believed that the use of antiplatelet therapy can have an increased risk of postoperative bleeding after cardiac and non-cardiac surgery. Patients with coronary stents in situ have a high risk of thrombotic risk if antiplatelet drugs are interrupted. Hence, there should be a balance between the risk of primary or recurrent thromboembolism if these drugs are stopped, against the risk of bleeding if these drugs are continued. (5)The withdrawal of aspirin in patients with coronary artery disease has been associated with a 2 to 4 fold increase in the risk of myocardial infarction and death.(6) This study has evaluated the effect of uninterrupted anti platelet therapy on the post-extraction bleeding following single dental extraction. A total of 50 patients with uninterrupted anti platelet therapy was observed for 30 minutes and 60 minutes post-extraction for bleeding, against 50 patients without any anti platelet therapy as the control group. In this study, 56% of the patients under anti platelet therapy were under the age group of 61-70 years with the mean age in the group being 60.2 ± 6.5 , which is in agreement with many other studies. (7),(8), (9),(10),(11)whereas in a study by Medeiros et al, the mean age was 57 years. The reason for the prevalence of cardiovascular diseases

increasing with age may be attributed to the diet, age changes like valve thickening and calcifications, and atherosclerotic burden. Among the patients in the case group, the majority of the patients (70%) on anti platelet therapy was found to be male, which is in accordance with many other studies. In a study by Paul S Myles et al, on patients who were scheduled to undergo coronary artery surgery, 83.3% were males. (12),(13),(14)Maas et al, stated that it is assumed that exposure to endogenous oestrogens during the fertile period of life delays the manifestation of atherosclerotic disease in women. In the Women's Ischemia Syndrome Evaluation (WISE) study it was shown that young women with endogenous estrogen deficiency have a more than sevenfold increase in coronary artery risk.(15). The increased incidence in males may be due to increased risk factors like diabetes, obesity, unhealthy diet, and smoking or alcohol usage. Majority of the patients in both the case and control groups, reported for extraction due to unrestorable carious teeth, 76% in case group and 74 % in control group. The prevalence of dental caries is found to be high in the patients belonging to low socio-economic status due to poor oral hygiene, lack of awareness, improper food habits and family status. (16) In this study, 66% of the patients were under single antiplatelet therapy with aspirin, 24 % under dual antiplatelet therapy and 10 % under clopidogrel. In Comparison with other studies, aspirin is the most widespread anti platelet agent in our population, followed by dual antiplatelet therapy and clopidogrel. A study by Ozge Doganay stated that the most common antiplatelet regimen in single antiplatelet therapy was aspirin (55.4%) followed by clopidogrel (9.9%) and ticagrelor (7.7%).(17),(18),(19). The antithrombotic properties of aspirin were recognized as early as in the 1950's, and it also has a lung protective effect after massive transfusion after cardiac surgery. The most common reason for anti platelet therapy has been found to be coronary artery disease in our study, accounting for 90%, followed by cerebrovascular accident and peripheral arterial disease. Bleeding was encountered in 4% of the patients on anti platelet therapy after 30 minutes of extraction in this study, which was controlled by applying pressure pack for 30 minutes further. There was no bleeding present after 60 minutes post- extraction in both case and control group. Bleeding was encountered in 2 patients on aspirin in this study which is similar to another study which showed 3.93% patients had post extraction prolonged immediate bleeding The bleeding was successfully controlled with pressure on gauze and no patient required suturing or re-hospital visit. There was no bleeding in the post extraction period at 24 and at 48 hours. (20) This was in contrast to many other studies which showed no bleeding in patients on aspirin, one of the study showed 4.2 % bleeding on combined anti-coagulant + aspirin, 2.8% anti-coagulant, and no bleeding in patients on aspirin (21), (22)Leon Ardekian et al, also demonstrated that dental extractions, even the more complex procedures, did not result in uncontrolled intraoperative or postoperative hemorrhage in patients receiving low-dose aspirin therapy on a long-term basis.(23) Patients undergoing minor dental, skin, or ophthalmic procedures can continue aspirin without any perioperative interruption. Evidence from small randomized trials and cohort studies suggest that the incidence of major bleeding is < 1% in patients continuing aspirin who underwent cataract removal, multiple tooth extractions, or benign dermatologic excisions.(24). Also a study by Hanken on patients with aspirin therapy undergoing oral osteotomy showed only 1.7% of bleeding post-operatively, which was controlled by local measures. (25) In this study, there was no bleeding noted in both clopidogrel and dual antiplatelet therapy. These results were in accordance with many other studies on dual antiplatelet therapy, where there was no bleeding noticed post-extraction. (26),(27). In a study by Aranza Canigral et al, 8% of the patients subjected to oral surgery suffered moderate bleeding. The risk of bleeding was significantly correlated to the ASPI test, and advanced age showed a near significant association to moderate bleeding risk(28). Most of the studies showed lower percentage on immediate post- extraction bleeding, and all of those were easily controlled by local hemostatic measures. (29)Some

earlier studies had stated doubt on the continuation of clopidogrel, as it was thought to cause bleeding complications post-operatively. Alexander Grobe conducted a clinical study on postoperative bleeding risk in osteotomy, which is an invasive surgery rather than simple extractions, under continued clopidogrel therapy. Nevertheless, the postoperative bleeding rates of 1.6% and 3.3% under continued mono- and dual clopidogrel therapy was found, which was controlled by local hemostatic measures.(30). Based on a review conducted by Joel Napenas et al on postoperative bleeding risk in dental patients on antiplatelet therapy, it is recommended that patients with drug eluting coronary artery stents be on dual antiplatelet therapy continuously for 12 months and that elective procedures where there is high risk of bleeding should be deferred until this course of antiplatelet therapy is completed. . Among patients with drug-eluting stents, 1 in 10 prematurely discontinue antiplatelet drugs within the first year, in many cases owing to dental procedures, leading to increased cardiovascular events, including myocardial infarction and death. (31) American Heart Association and American College of Cardiology and Cardiac Society of Australia and New Zealand have emphasized the potential complications of pre operative anti platelet discontinuation and stated that minor dental operations, tooth extractions, and prophylaxis could be performed with acceptable bleeding risks. European Society of Cardiology and European Society of Anesthesia also recommended that surgery can be performed without interrupting current antiplatelet medication therapy whenever possible. Also, it is stated that sudden withdrawal of antiplatelet drugs in chronic users may produce a rebound prothrombotic effect due to increased thromboxane A2 synthesis and decreased fibrinolysis. It has been observed that post-extraction bleeding can be effectively managed by local hemostatic measures like gauze compression, suturing, tranexamic acid, absorbable gelatin sponge, electrocautery and fibrin sealants, which is in accordance with many other studies.(32), (33),(34),(35) Bleeding that has been encountered in this study may be due to acute inflammation associated with the extracted tooth or presence of granulation tissue. A study by Gerotra, stated that factors that aggravate the postoperative bleeding were multiple extractions/third molar extraction, flap surgery, acute inflammation, presence of granulation tissue, periodontitis, and pericoronitis. Excessive tension during flap surgery leads to opening of sutures and bleeding, Stress induced hypertension was also an attributing factor in the elderly patients. (36)

LIMITATIONS

Main drawback of this study would be the small sample size involved and also the inclusion of only single dental extraction. Therefore, our results cannot be generalized to more complex cases with multiple extractions. This study included only the most commonly used antiplatelet drugs, like aspirin and clopidogrel. Hence the safety of other antiplatelet agents like prasugrel, ticagrelor or ticlopidine was not assessed. Platelet aggregation test was not performed in this study to evaluate the effect of antiplatelet drugs on platelet, since it was considered to be expensive and also the importance or relevance of the test is also not well documented in the previous studies.

INTERPRETATION

According to previous studies, sample size was calculated as 8 in each group. All patients satisfying the research criteria who reported to the department of OMFS were studied. A total of 50 patients were studied in each group. Both the groups of patients were observed for 30 minutes and 60 minutes post-extraction.

GENERALISABILITY

It can be considered that interruption of antiplatelet therapy prior to single dental extraction is not necessary since there is no large risk of hemorrhage.

CONCLUSION

Use of oral antiplatelet medications has been rising steadily in recent years due to the high incidence of cardiovascular diseases in the present era. Management of patients on antiplatelet therapy requiring extractions is still considered to be a controversy. The decision to continue the antiplatelet medications for the fear of cardiac events or interruption of the medications prior to dental extractions in view of bleeding, still remains doubtful to many practitioners. Hence, this study was conducted to evaluate the effect of uninterrupted antiplatelet therapy on post extraction bleeding. According to the results of this study, stoppage of antiplatelet therapy prior to dental extraction is not necessary and is not associated with any risk of hemorrhage. Bleeding, if present, from the extraction sites can be managed by local hemostatic measures. However, further studies are required to justify the application of this on patients with higher doses of antiplatelet therapy, other types of antiplatelet medications other than aspirin and clopidogrel, for multiple antiplatelet drug therapy and for those undergoing more invasive dental surgery.

ACKNOWLEDGEMENTS

Dr Ajithkumar K, HOD, Dept of Oral and Maxillofacial Surgery, Govt. Dental college, Trivandrum, Kerala.

REFERENCES

1. Sushma K, Shetty J, Pandey V, Mukherjee S, Kumar S. Dental Extractions in Patients on Antiplatelet Therapy: A Clinical Study. *IJRSMS*. 2017 Jun;03(01):034–9.
2. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal. *Journal of the American College of Cardiology*. 2005 Feb;45(3):456–9.
3. Minassian C, D’Aiuto F, Hingorani AD, Smeeth L. Invasive Dental Treatment and Risk for Vascular Events: A Self-Controlled Case Series. *Ann Intern Med*. 2010 Oct 19;153(8):499.
4. Saez-Alcaide L, Sola-Martin C, Molinero-Mourelle P, Paredes-Rodriguez V, Zarrias-Caballero C, Hernandez-Vallejo G. Dental management in patients with antiplatelet therapy: A systematic review. *J Clin Exp Dent*. 2017;0–0.
5. Gerstein NS, Schulman PM, Gerstein WH, Petersen TR, Tawil I. Should More Patients Continue Aspirin Therapy Perioperatively?: Clinical Impact of Aspirin Withdrawal Syndrome. *Annals of Surgery*. 2012 May;255(5):811–9.
6. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Stopping vs. Continuing Aspirin before Coronary Artery Surgery. *N Engl J Med*. 2016 Feb 25;374(8):728–37.
7. Eapen BrigitV, Baig MF, Avinash S. An Assessment of the Incidence of Prolonged Postoperative Bleeding After Dental Extraction Among Patients on Uninterrupted Low Dose Aspirin Therapy and to Evaluate the Need to Stop Such Medication Prior to Dental Extractions. *J Maxillofac Oral Surg*. 2017 Mar;16(1):48–52.
8. Napeñas JJ, Oost FCD, deGroot A, Loven B, Hong CHL, Brennan MT, et al. Review of postoperative bleeding risk in dental patients on antiplatelet therapy. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2013 Apr;115(4):491–9.
9. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of Discontinuing Aspirin Therapy on the Risk of Brain Ischemic Stroke. *Arch Neurol*. 2005 Aug 1;62(8):1217.
10. Brennan MT, Valerin MA, Noll JL, Napeñas JJ, Kent ML, Fox PC, et al. Aspirin Use and Post-operative Bleeding from Dental Extractions. *J Dent Res*. 2008 Aug;87(8):740–4.
11. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. DOES LOW-DOSE ASPIRIN THERAPY COMPLICATE ORAL SURGICAL PROCEDURES? *The Journal of the American Dental Association*. 2000 Mar;131(3):331–5.

12. Duygu G, Ozcakir-Tomruk C, Guler N, Sencift K. Assessment of Effects of Antiplatelet Drugs on Bleeding Risk After Teeth Extractions. *Biotechnology & Biotechnological Equipment*. 2010 Jan;24(3):2040–3.
13. Gröbe A, Fraederich M, Smeets R, Heiland M, Kluwe L, Zeuch J, et al. Postoperative Bleeding Risk for Oral Surgery under Continued Clopidogrel Antiplatelet Therapy. *BioMed Research International*. 2015;2015:1–4.
14. Finkel JB, Marhefka GD, Weitz HH. Dual Antiplatelet Therapy With Aspirin and Clopidogrel: What Is the Risk in Noncardiac Surgery? A Narrative Review. *Hospital Practice*. 2013 Feb;41(1):79–88.
15. Park M-W, Her S-H, Kwon JB, Lee JB, Choi M-S, Cho JS, et al. Safety of Dental Extractions in Coronary Drug-Eluting Stenting Patients Without Stopping Multiple Antiplatelet Agents. *Clin Cardiol*. 2012 Apr;35(4):225–30.
16. Metzler H, Kozek-Langenecker S, Huber K. Antiplatelet therapy and coronary stents in perioperative medicine – the two sides of the coin. *Best Practice & Research Clinical Anaesthesiology*. 2008 Mar;22(1):81–94.
17. Ferreira-González I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, et al. Double Antiplatelet Therapy After Drug-Eluting Stent Implantation. *Journal of the American College of Cardiology*. 2012 Oct;60(15):1333–9.
18. Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, et al. Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents. *Journal of the American College of Cardiology*. 2007 Feb;49(6):734–9.
19. Lillis T, Ziakas A, Koskinas K, Tsirlis A, Giannoglou G. Safety of Dental Extractions During Uninterrupted Single or Dual Antiplatelet Treatment. *The American Journal of Cardiology*. 2011 Oct;108(7):964–7.
20. Dézsi BB, Koritsánszky L, Braunitzer G, Hangyási DB, Dézsi CA. Prasugrel Versus Clopidogrel: A Comparative Examination of Local Bleeding After Dental Extraction in Patients Receiving Dual Antiplatelet Therapy. *Journal of Oral and Maxillofacial Surgery*. 2015 Oct;73(10):1894–900.
21. Sanchez-Palomino P, Sanchez-Cobo P, Rodriguez-Archilla A, Gonzalez-Jaranay M, Moreu G, Calvo-Guirado JI, et al. Dental extraction in patients receiving dual antiplatelet therapy. *Med Oral*. 2015;e616–20.
22. Bajkin BV, Urosevic IM, Stankov KM, Petrovic BB, Bajkin IA. Dental extractions and risk of bleeding in patients taking single and dual antiplatelet treatment. *British Journal of Oral and Maxillofacial Surgery*. 2015 Jan;53(1):39–43.
23. Olmos-Carrasco O, Pastor-Ramos V, Espinilla-Blanco R, Ortiz-Zárate A, García-Ávila I, Rodríguez-Alonso E, et al. Hemorrhagic Complications of Dental Extractions in 181 Patients Undergoing Double Antiplatelet Therapy. *Journal of Oral and Maxillofacial Surgery*. 2015 Feb;73(2):203–10.
24. Manoharan S, Sadhanandan M, Varghese Kg. Evaluation of bleeding following dental extraction in patients on long-term antiplatelet therapy: A clinical trial. *Indian J Dent Res*. 2015;26(3):252.
25. Lu S-Y, Tsai C-Y, Lin L-H, Lu S-N. Dental extraction without stopping single or dual antiplatelet therapy: results of a retrospective cohort study. *International Journal of Oral and Maxillofacial Surgery*. 2016 Oct;45(10):1293–8.
26. Sadeghi-ghahrody M, Yousefi-malekshah SH, Karimi-sari H. Bleeding after tooth extraction in patients taking aspirin and. *British Journal of Oral & Maxillofacial Surgery*. 2016;(March).
27. Schreuder WH, Peacock ZS. Antiplatelet therapy and exodontia. *The Journal of the American Dental Association*. 2015 Nov;146(11):851–6.

28. Verma G. Dental Extraction Can Be Performed Safely in Patients on Aspirin Therapy: A Timely Reminder. *ISRN Dentistry*. 2014 Apr 1;2014:1–11.
29. Wahl MJ. Dental Surgery and Antiplatelet Agents: Bleed or Die. *The American Journal of Medicine*. 2014 Apr;127(4):260–7.
30. Dézsi CA, Dézsi BB, Dézsi AD. Management of dental patients receiving antiplatelet therapy or chronic oral anticoagulation: A review of the latest evidence. *European Journal of General Practice*. 2017 Oct 2;23(1):197–202.
31. Daniel NG, Goulet J, Bergeron M, Paquin R, Landry P-E. Antiplatelet drugs : is there a surgical risk? *J Can Dent Assoc*. 2002 Dec;68(11):683–7.
32. Sadhasivam G, Bhushan S, Chiang KC, Agarwal N, Vasundhar PL. Clinical Trial Evaluating the Risk of Thromboembolic Events During Dental Extractions. *J Maxillofac Oral Surg*. 2016 Dec;15(4):506–11.
33. Hong C. Hong C. UvA-DARE (Digital Academic Repository) Oral antithrombotics and dentistry: Current state of affairs and guideline proposal van Diermen, D.E. 2019; 2019. 2019;
34. McCullough M. Dental note: Antiplatelet drugs, anticoagulants and elective surgery. *Aust Prescr*. 2011 Oct 1;34(5):143.
35. Koskinas KC, Lillis T, Tsirlis A, Katsiki N, Giannoglou GD, Ziakas AG. Dental Management of Antiplatelet-Receiving Patients: Is Uninterrupted Antiplatelet Therapy Safe? *Angiology*. 2012 May;63(4):245–7.
36. Oprea AD, Popescu WM. Perioperative management of antiplatelet therapy. *British Journal of Anaesthesia*. 2013 Dec;111:i3–17.