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Comparative assessment of post-operative bleeding after tooth extraction in patients on antiplatelet therapy

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Abstract

Objectives: To assess postoperative bleeding after tooth extraction in patients on various antiplatelet therapies.

Material and Methods: A total of 150 patients to undergo teeth extractions who were on various antiplatelet therapies were divided randomly into 3 equal groups. Group 1 (50 patients) were the patients on Mono antiplatelet therapy, Group 2 (50 patients) were the patients on Dual antiplatelet therapy, and Group 3 (50 patients) were the patients who have discontinued antiplatelet therapy 1 week before tooth extraction. Bleeding Time of all the patients was recorded before the tooth extraction procedure, and after the extraction was done. Statistical analysis between the three groups was done after 1st hour, 24th hour and 48th hour.

Results: The results showed statistically significant value ($p < 0.05$), when bleeding status was checked at 1st hour after tooth extraction in all 3 groups. At 24th hour and 48th hour, the bleeding status amongst the 3 groups reported no significant difference.

Conclusion: Antiplatelet therapy (mono/dual) needs no alteration or stopped before tooth extraction, as the postoperative bleeding can be easily controlled by local hemostatic measures. Antiplatelet therapies have minimal impact on the bleeding status following routine tooth extraction.

Keywords: Antiplatelet therapy; Bleeding time; Tooth extraction

Introduction

Hemostasis is the mechanism that impedes blood loss through fibrin formation (clotting), occurring in three phases:

- Vascular phase: neurogenic vasoconstriction decreasing the escape of blood;

- Platelet phase: platelet aggregation occurs;
- Plasma coagulation phase: fibrin clotting.[1]

Platelets provide the initial hemostatic plug at the site of vascular injury, and they are involved in pathological processes and are an important contributor to arterial thrombosis, leading to myocardial infarction and ischemic stroke.[2]

Antiplatelet drugs are used for treatment and as prophylactic measures for various cardiovascular diseases and cerebrovascular accidents for thromboembolic disorders. They are indicated in cases of arterial thrombosis, ischemic heart disease (acute is chaemic stroke, transient ischemic attacks), previous myocardial infarction, post-coronary artery bypass grafting surgery, post percutaneous coronary intervention (PCI) with stenting, atrial fibrillation with a high risk of stroke, post percutaneous intervention of peripheral arterial disease, stable angina, and primary prevention of coronary artery disease, colon cancer and venous thromboembolism.[3,4]

Ischemia in heart, lungs, and brain is preceded mainly by thrombotic and thromboembolic occlusion of blood vessels, which are rich in platelets. Over time, numerous antiplatelet agents have been developed with a multitude of indications and used as potential therapies for the prevention and management of arterial thrombosis.[5]

Antiplatelet medications divide into oral and parenteral agents, and oral agents subdivide further based on the mechanism of action. Aspirin was the first antiplatelet medication and is a cyclooxygenase inhibitor. Other oral antiplatelet agents include clopidogrel, ticagrelor, prasugrel, pentoxifylline, cilostazol, and dipyridamole, while parenteral agents include tirofiban and eptifibatide. The most commonly used antiplatelet drugs include aspirin and clopidrogel.[6] Clopidogrel is superior to aspirin for the prevention of the combined risk of cerebrovascular accident, acute myocardial infarction, and cardiovascular mortality. However, on analyzing individual complications, it was found that clopidogrel is beneficial in the patient group with symptomatic peripheral arterial disease. Due to different action mechanisms of Aspirin and clopidogrel, it is reported that this combination boosts the prevention of cardiovascular complications.[1]

When a patient on antiplatelet therapy (APT) needs to undergo minor oral surgical procedures, the surgeon is confronted with the choice of interrupting the therapy, which increases the risk of thrombosis or continuing the medication which increases the risk of haemorrhage.[7] Knowledge of the pharma codynamics and pharma cokinetics may allow practitioners to anticipate difficulties associated with drug withdrawal and administration in the perioperative period including the potential for drug interactions. Though the previous studies have shown very few complications associated with minor oral surgical procedure without interruption of antiplatelet drugs,[8] there are very few literature studies to support the findings. Hence, the present study was conducted to assess postoperative bleeding after dental extraction among patients on antiplatelet therapy.

Materials and methodology

Study method and design

A sequential enrollment of 150 patients on Antiplatelet Therapy (APT) reporting from January 2020 to January 2022 in the Department of Oral and Maxillofacial Surgery, for the teeth extractions was done with an informed/written consent.

A. Prospective, randomized, double blinded study.

B. The participants were randomly divided by computer-generated randomization list into three groups of 50 each:

Group 1: Patients on Mono APT (Aspirin)

Group 2: Patients on Dual APT (Aspirin and Clopidogrel)

Group 3: Patients who had discontinued APT 1 week before tooth extraction.

Inclusion Criteria

1. Patients on APT who reported for tooth extraction, in the age group of 25 – 45 years.
2. Patients fit for extractions under local Anesthesia.

Exclusion Criteria

1. Bleeding time of the patients above normal values.
2. Patients with confounding variables such as on medications which alter the action of the antiplatelet drugs and patients who were known cases of liver disease.
3. Patients with history of uncontrolled bleeding episodes.
4. Patients with grossly carious or impacted tooth, qualifying for trans alveolar extractions.

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (SDDHDC/IEC/2021/28) and with the 1964 Declaration of Helsinki and its later amendments of 2013 or comparable ethical standards.

Surgical Overview

A detailed case history, which included age, gender, and systemic conditions for which APT was prescribed, was recorded for all the patients enrolled in the study. The name of antiplatelet drug and its dosage frequency was also noted down. Bleeding time (Dukes method) was checked preoperatively for all the patients and those with normal bleeding time between 2 and 5 min were taken up for surgery.

In all the three groups, tooth indicated for simple extraction under local anesthesia was done, followed by placement of pressure pack at extraction socket. Patients were monitored for checking the type of bleeding (absence or presence of bleeding, oozing, and active bleeding) at socket in the 1st hour at the center and a telephonic review of all the patients was done at 24th hour and 48th hour. Oozing is considered when blood completely turns the pack into red but does not fill the mouth with blood. Active bleeding is considered when the socket bleeding fills the mouth with blood frequently. Local hemostatic agents such as oxidized cellulose/Gel foam pack/bone wax were used in cases of uncontrolled bleeding. All the participants in the study were asked to contact, in case of any uncontrolled bleeding after discharge.

Outcome Parameters

All patients from Group 1, Group 2 and Group 3 were compared for:

1. Bleeding Time after extraction and with respect to Age and Duration of antiplatelet (aspirin and/ or clopidogrel) therapy and the Type of Anti Platelet Therapy administered.
2. Comparison of Bleeding Status at 1st hour, 24th hour and 48th hour after tooth extraction.

Data was analyzed using the statistical package SPSS 22.0 (SPSS Inc., Chicago, IL) with the Chi-square test and level of significance was set at $p<0.05$.

Results

A total of 150 patients in the age group of 25 to 45 years were evaluated of whom 62% of patients were male and 38% of patients were female. The mean age (in years) of the patients were 39 in Group 1, 33.26 in Group 2 and 36.08 in Group 3. The mean duration (in months) of the APT in patients were 36.08 for Group 1, 34.10 for Group 2, and 32.41for Group 3. Of the 150 patients, 39% of the patients were on Mono APT (Group 1) which comprised acetylsalicylic acid (Aspirin), 21% of the patients were on Dual APT (Group 2) of acetylsalicylic acid along with

clopidogrel, and 40 % of the patients had discontinued APT (mono/dual) 1 week before tooth extraction. The results were not statistically significant ($p > 0.05$) as illustrated in Table 1.

Bleeding Time (in seconds) in all 3 groups were compared for before and after tooth extractions and the results were not statistically significant, as shown in Table 2.

None of the patients in the three groups showed active bleeding at all postoperative intervals (1st hour, 24th hour and 48th hour). Oozing was seen in 6 patients in Group 1, 9 patients in Group 2 and 8 patients in Group 3, when checked at 1st hour after tooth extraction. At 24th hour, oozing was seen in 1 patient in Group 1, 2 patients in Group 2 and 1 patient in Group 3. At 48th hour interval, none of the patients in all 3 groups exhibited post-operative bleeding (oozing). Comparision of bleeding at different time intervals in all 3 groups was analyzed with Chi-square test. At 1st hour interval, the result was statistically significant ($p < 0.05$), when compared amongst the 3 groups, while no significant differences ($p > 0.05$) were observed at 24th – 48th hour interval (Table 3).

Table 1: Comparision of age, duration of antiplatelet therapy

Variables	Groups	Mean	Standard Deviation	P value
Age (Years)	Group 1	39	9.65	0.208
	Group 2	33.26	9.54	
	Group 3	36.08	8.77	
Duration (Months)	Group 1	36.08	6.31	0.408
	Group 2	34.1	6.87	
	Group 3	32.41	7.28	

($p > 0.05$ – Not Significant)

Table 2: Comparision of bleeding time (in seconds)

Variables	Groups	Before Extraction	After Extraction	P value
Mean ± standard deviation	Group 1	77.23 ± 17.66	77.55 ± 13.65	0.208
	Group 2	78.37 ± 13.15	73.27 ± 19.85	
	Group 3	76.85 ± 15.46	77.83 ± 12.99	

($p > 0.05$ – Not Significant)

Table 3: Comparision of bleeding status at different time intervals

Variables	Groups	1st hour	24th hour	48th hour
Oozing sites (Present – p, absent – a)	Group 1 (n=50)	6 P, 44 A	1 P, 49 A	0 P, 50 A
	Group 2 (n=50)	9 P, 41 A	2 P, 48 A	0 P, 50 A
	Group 3 (n=50)	8 P, 42 A	1 P, 49 A	0 P, 50 A
P value		0.029*	0.119	0.102

(*$p < 0.05$ – Significant at 1st Hour)

Discussion

Maxillofacial surgeons are exposed to patients on antiplatelet drugs to prevent arterial thrombosis. A major concern in such patients is the management of potentially excessive bleeding post minor oral surgical procedures.

Oral surgical procedures in patients on antiplatelet therapy must be decided according to the nature and severity of the disorder and extent of the proposed surgical treatment plan. The main management goal in such patients is to allow adequate local haemostasis. Without adequate management, hemorrhage and hematoma can lead to airway obstruction, thus placing the patient's life in danger. The relevant ways to achieve haemostasis are to minimize trauma; to avoid flaps; to use surgical techniques that facilitate suturing; cauterization; and the granulation tissue removal from

areas of chronic inflammation.[1] Haemostasis primarily depends on vascular and platelet-mediated event (platelet plug formation and secondarily complex cascade of clotting factors).[9] Platelets are involved in various thrombotic processes; drugs that inhibit platelet function have assumed increased importance in the care of patients with cardiovascular and cerebrovascular diseases.[10]

Antiplatelets can be classified[11,12] based on the mechanism of action as follows:

1. Platelet aggregation inhibitors such as;

a. Aspirin and related cyclooxygenase inhibitors

b. Oral thienopyridines such as clopidogrel, ticagrelor, ticlopidine, and prasugrel

2. Glycoprotein platelet inhibitors (e.g., abciximab, eptifibatide, tirofiban)

3. Protease-activated receptor-1 antagonists (e.g., vorapaxar)

4. Miscellaneous (e.g., dipyridamole - a nucleoside transport inhibitor and phosphodiesterase type 3 (PDE3) inhibitor, cilostazol - also a PDE3 inhibitor)

Aspirin is the most studied, most commonly used, most clinically effective and the least expensive oral antiplatelet drug. It works by irreversibly inhibiting the cyclooxygenase enzyme (COX) activity in the prostaglandin synthesis pathway (PGH2). This prostaglandin is a precursor of thromboxane A2 (TXA2) and PGI2. Thromboxane A2 works by inducing platelet aggregation and vasoconstriction, and COX-1 mediates its production, while PGI2 works by inhibiting platelet aggregation and induces vasodilation, and is mediated by COX-2. Low-dose aspirin (75 mg/day to 150 mg/day) can induce complete or near-complete inhibition of COX-1, thus inhibiting the production of TXA2, while larger doses (up to 325 mg/day) are required to inhibit COX-2.[13]

Oral thienopyridines such as clopidogrel selectively inhibit adenosine diphosphate-induced (ADP-induced) platelet aggregation. These drugs are converted into the active drug with the help of the hepatic CYP450 system that can irreversibly inhibit the platelet P2Y12 receptor. The usual dose is 75 mg/day.[14]

Glycoprotein platelet inhibitors work by inhibiting glycoprotein IIb/IIIa (GpIIb-IIIa) receptors on platelets, thus decreasing platelet aggregation, and most commonly used in Acute Coronary Syndrome. These drugs are only available in an intravenous form and are therefore used as short-term therapy.[12]

Dipyridamole has antiplatelet and vasodilating properties and inhibits platelet cyclic nucleotide phosphodiesterase, which increases intra-platelet cyclic AMP accumulation and inhibits platelet aggregation. It also blocks the uptake of adenosine by the platelets, which also increases cyclic AMP.[15]

Cilostazol is also reported to have vasodilatory, antiplatelet properties, and antiproliferative effects. It also reduces smooth muscle cell hyperproliferation and intimal hyperplasia after an injury to the endothelium.[16]

This study was undertaken to evaluate antiplatelet therapy on bleeding after tooth extraction. The study compared BT in patients on mono and dual APT with those who discontinued it 1 week before extraction. In our study, all three groups were compared for BT after extraction and with respect to age and duration of antiplatelet therapy.

In our study, none of the patients in the three groups showed active bleeding at all postoperative intervals (1st hour, 24th hour and 48th hour). This finding was supported by the individual studies of Babaji and Rishal[17], and Hoda MM et al.,[18] who evaluated the need for stoppage of Dual APT in patients undergoing dental extractions, and reported no active bleeding at 1st hour to

48th hour interval. In the present study, oozing was seen in all 3 groups when checked at 1st hour and 24th hour after tooth extraction. At 48th hour interval, none of the patients in all 3 groups exhibited post-operative bleeding (oozing). The result was statistically significant only at 1st hour when compared amongst the 3 groups. There was no significant uncontrolled bleeding after dental extraction in all three groups. Our study results are in concurrence with results of Lemkin et al., and Mc Gaul et al., who documented significant results of postoperative bleeding at 1st hour after dental extraction. Our results are also supported by the study of Girotra C et al.,[19] and Hoda MM et al.,[18] who found that risk of bleeding in the immediate postoperative period (1st hour) was higher with patient on Dual APT. Similar study by Babaji and Rishal[17] assessed the risk of post operative bleeding among patients on APT, and reported no significant risk of bleeding at 1st to 24th hour interval.

Studies by Bajkin et al.,[20] Varghese et al.,[21] Karsl et al.,[22] and Cardona-Tortajada et al.,[3] from their studies confirmed that dental extraction can be done without a significant risk of bleeding in patients on Mono APT. Another study by Madan GA et al.,[23] concluded that most minor oral surgical procedures can be safely carried out without stopping long-term low-dose aspirin regimen. Sanchez-Poalomino et al.,[1] and Sadeghi-Ghahrody et al.,[8] in their individual studies concluded that the use of Dual APT had no considerable effect on the risk of bleeding in patients with conventional forcep extractions. In our study, Group 3 patients were selected in accordance to the studies by Sonic et al.,24 Mc Gaul et al.,25 Daniel et al.,26 where they recommended stopping APT 7 days preoperatively. The rationale for such recommendation was that, after 3 days of interruption of aspirin, sufficient number of newer platelets will be present in the circulation for effective hemostasis.[27] A study by Dara wade DA et al.,[28] concluded that in patients on Mono APT as well as APT discontinuing group, bleeding time and clotting time remained within the normal limits. Similar results are reported in the study by Doganay O et al.,[29] where among patients on Mono and/or Dual APT, none experienced prolonged postoperative bleeding.

New class of oral anticoagulants (NOACs) such as dabigatran (Pradaxa), apixaban (Eliquis), and rivaroxaban (Xarelto) are recently introduced for the treatment and prevention of thromboembolism. NOACs are novel direct-acting medications that are selective for one specific coagulation factor (key proteases), such as dabigatran (a direct inhibitor of Factor IIa-Thrombin) and rivaroxaban, apixaban, and edoxaban (direct inhibitors of activated factor X a). NOACs function unlike traditional Vitamin K Antagonist (VKA), which prevent the coagulation process by suppressing the synthesis of vitamin K-dependent factors. The important indications of these drugs are the prevention and treatment of deep vein thrombosis and pulmonary embolisms, and atherothrombotic events in the heart and brain of patients with acute coronary syndrome and atrial fibrillation. Their dosage isn't fixed and various dosages are available for purchase.[30]

Literature studies have reported multiple advantages for NOACs when compared with VKAs, with the most important advantages being safety issues (i.e., a lower incidence of major bleeding), convenience of use, minor drug and food interactions, a wide therapeutic window, and no need for laboratory monitoring. One major disadvantage of the new drugs compared to warfarin was the lack of a reversal agent to help deal with uncontrollable bleeding, which is recently changed with the approval of idarucizumab, a humanized monoclonal antibody against dabigatran.[31] Parenteral idarucizumab can be given when rapid reversal of dabigatran is required

for emergency surgery or urgent life-threatening procedures or uncontrolled bleeding. Antidotes for the other new drugs are not yet available.

A systemic review by Suez-Alcaide LM et al.,[32] on the dental management of patients under antiplatelet treatment concluded that the current trend is to maintain the treatment during the surgical procedure,assuring a good control of the haemorrhage with local hemostatic measures.

In the present study, it was observed that dental extractions can be done safely in patients on antiplatelettherapy without altering or modifying its dose to avoid complications of thromboembolism and provided that there should be sufficient local measures to control postoperative bleeding. It is to be noted that infiltration or intraligamentary injection should be administered wherever practical, and regional nerve blocks should be avoided.[33]

The procedure should be atraumatic and any postoperative bleeding should be managed using local haemostatic measures.

Conclusion

The long-standing dogma concerning the higher risk for bleeding during and after dental procedures results in stopping antiplatelet medications before a procedure causes unnecessary deferral of dental care. This study concludes that APT needs not be stopped, before routine extraction procedures.

Practical Implications

Antiplatelets are used for the prevention of myocardial infarction, ischemic stroke, and vascular death among patientswho are at high risk of these events. The benefits of use of antiplatelet drugs by patients outweigh the risk of postoperative bleeding.

Limitations

The limitations of this study are lesser sample size and further studies to assess the role of various APT on different oral surgical procedures is needed. With the advent of new antiplatelet regimens, it is necessary that they are studied and their risks in dental extractions procedure are to be assessed which is a limitation of our study.

Scientific Rationale for study

This study is to make the readers aware about anti-platelet therapy and its effects on minor oral surgical procedures including surgical extraction. Mono platelet and Dual platelet therapy have their own indications and contraindications, though their discontinuation prior to minor oral surgical procedures doesn't have any additional benefits; neither the continuation caused any deficit in the study groups.

Principle Findings

The findings suggest that antiplatelets have minimal impact on the amount and duration of bleeding following routine dental extractions.

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