Clinical Trial Evaluating the Risk of Thromboembolic Events During Dental Extractions

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Abstract

Purpose Discontinuation of anti-platelet therapy increases the risk of thrombotic complications whereas its continuation is believed to increase the risk of prolonged post-extraction bleeding. We therefore, performed this study to evaluate the risk of significant bleeding following dental extractions and also to assess the necessity of discontinuing anti-platelet therapy.

Patients and methods Three hundred patients requiring dental extraction were included in the study in which 200 patients were on anti-platelet therapy. Patients were divided into three groups of 100 patients each. Group 1 consisted of patients continuing their anti-platelet therapy, Group 2 consisted of patients whose anti-platelet therapy was interrupted and Group 3 comprised of healthy patients not on anti-platelet therapy. Preoperative bleeding and clotting time were determined for all patients. The procedure involved single or multiple teeth (>3 teeth) extractions under local anesthesia with a vasoconstrictor. Pressure pack was given in all cases as in routine dental extractions and bleeding was checked after 15, 30 min, 1, 24, 48 h and 1 week. Immediate post-extraction bleeding was considered to be prolonged if it continued beyond 30 min in spite of the pressure pack. Late and very late bleeding was considered to be clinically significant if it extended beyond 12 and 24 h respectively.

Results The mean bleeding time in Groups 1, 2, and 3 were 1 min and 32 s, 1 min and 25 s, and 1 min and 27 s, respectively. Prolonged immediate post-extraction bleeding (bleeding after 30 min) was present among 9 patients in Group 1 (9 %) and 15 patients in Group 2 (15 %) whereas it was not seen in any patient of Group 3. Bleeding after 1 h was present in 9 patients of Group 2 (9 %) and was controlled with gelatin sponge within half an hour thereafter. None of the patients in any group reported with bleeding after 24, 48 h and 1 week.

Conclusion Dental extractions can be safely carried out in patients on anti-platelet therapy without the risk of significant post-extraction bleeding thus averting the risk of thromboembolic events that might take place on temporary discontinuation of antiplatelet therapy.

Keywords Anti-platelet therapy · Dental extraction · Thromboembolic events · Aspirin and clopidogrel

Introduction

Modernization of lifestyle has unfortunately brought in with it various medically compromising conditions such as cerebrovascular and cardiovascular thromboembolic disorders. These conditions, however, are of more concern to Oral and Maxillofacial Surgeons, as these patients are maintained on long term prophylactic/therapeutic anti-platelet agents like aspirin and clopidogrel which inhibits platelet aggregation. Like a double edged sword, anti-platelet agents have also got its own advantages and limitations. Incidences of intra-operative and post-operative bleeding may be increased while treating these patients because of its effect on reducing platelet aggregation whereas stopping these drugs may expose the patients to

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the risk of thromboembolic events like cerebrovascular accidents and myocardial infarction. However, risk of excessive bleeding following dental extractions should always be balanced against the risk of thrombotic event.

The optimal dental management of such patients is not clearly defined since the amount of blood loss depends on the invasiveness of the surgical procedure and no surgical interventions are alike. Therefore, dental surgeons are most of the times faced with dilemma whether to continue or stop such medications during extraction procedures. Murphy et al. [1] in their survey, found that 90 % of the respondents which included general dental practitioners stopped the anti-platelet agent prior to dental extractions and Alcock et al. [2] found that the decision to cease anti-platelet therapy, which occurred in almost half of their study population, was not guided by peri-operative cardiac risk stratification. This shows that there is lack of awareness among dentists regarding management of patients on anti-platelet drugs [3]. Hence, there is a clear need for greater awareness of an evidence based approach to the management of these patients before undertaking extraction procedures to avoid unnecessary complications.

There are very few studies in the literature comparing post-extraction bleeding in patients who continued anti-platelet therapy during extraction to that of the patients who discontinued the therapy and to a healthy control group, in such a large number of patients and further fewer studies have been done to evaluate the difference between patients on monotherapy and dual therapy. We therefore, performed a study to evaluate the difference in post-extraction bleeding among anti-platelet stopping group, non-stopping group and healthy control group and also related it to the type of therapy, mono/dual therapy.

Patients and Methods

Our Ethical and Research Committee approved the study, conducted in the Department of Oral and Maxillofacial Surgery, GITAM Dental College and Hospital, Andhra Pradesh, India. A detailed written informed consent was obtained from the patients in English and vernacular language. A total of 300 patients requiring dental extractions were included in the study and were divided into three groups. Of them, 200 were on anti-platelet therapy (single/dual) for various cardiac ailments and were allocated randomly either into Group 1 or 2 whereas Group 3 comprised of 100 healthy patients not taking any hemostasis altering medication.

Group 1 (Non-stopping group) 100 patients (86 males and 14 females) who continued anti-platelet therapy during dental extractions.

Group 2 (Stopping group) 100 patients (88 males and 12 females) who discontinued anti-platelet therapy 3–5 days prior to dental extractions and resumed their medication 2 days post-extraction.

Group 3 (control group) 100 healthy patients (45 males and 55 females) who were not on any hemostasis altering medications.

Group 2 patients were referred to physician/cardiologist for a written consent regarding discontinuation of anti-platelet therapy during dental extraction. All patients underwent estimations of bleeding time and clotting time on the day of extractions. Patients with a pre-operative bleeding time of more than 10 min, a history of systemic conditions like liver disease, bone marrow disorders, patients who were on any hemostasis altering medications other than anti-platelet drugs, patients with a systolic blood pressure above 150 mm of Hg or a diastolic blood pressure above 100 mm of Hg and medically compromised patients who were not fit to undergo dental extraction procedures under local anesthesia were excluded from the study.

Extractions (single or multiple teeth) were performed under local anesthesia using 2 % lignocaine hydrochloride with a vasoconstrictor (1:80,000 adrenaline). Following extraction, a pressure pack was given and patient was kept under observation. Presence or absence of bleeding at the extraction site was checked at 15, 30 min, 1, 24, 48 h and 1 week after extraction.

At mentioned time intervals the extraction site was observed and bleeding that extended beyond the socket within 1 min was recorded as a positive result for bleeding at that time interval. In case of persistent bleeding beyond 1 h, local hemostatic agent, gelatin sponge was inserted into the extraction socket in order to achieve hemostasis. After ensuring hemostasis, patients were discharged with postoperative instructions and were prescribed amoxicillin 500 mg and paracetamol 500 mg, thrice daily for 5 days. They were advised to inform by person or through phone immediately in case of any post-operative bleeding.

In this study, we classified post-extraction bleeding as immediate, late and very late. Immediate post-extraction bleeding was considered to be prolonged if it continued beyond 30 min in spite of the pressure pack. Late bleeding was considered to be clinically significant if it extended beyond 12 h, or made the patient call or return to the surgeon or emergency department, or resulted in hematoma or ecchymosis within the oral soft tissues or which required blood transfusion. Very late bleeding was considered present if oozing occurred even after 24 h.

Chi square test and ANOVA test was used to evaluate results among the three groups and determine statistical significance, if any.

Results

A total of 300 patients were included in the study. Groups 1 and 2 comprised of patients who either continued or stopped anti-platelet therapy during extractions and Group 3 served as control group comprising healthy patients. The two treatment groups were similar in terms of number of patients on monotherapy and dual therapy with the difference being statistically insignificant (p value = 0.102). Table 1 shows distribution of patients based on the type of therapy.

The BT estimates among patients in Group 1 ranged from 1 min and 10 s to 3 min (mean 1 min and 32 s), whereas in Group 2, this range was from 1 min and 7 s to 2 min and 30 s (mean 1 min and 25 s). Group 3 BT values ranged from 1 min and 20 s to 2 min and 10 s (mean 1 min and 27 s). All these values were within acceptable limits and no statistically significant difference was observed among the three groups.

Events of single or multiple tooth extractions were also similar among the three groups. Table 2 shows the number of teeth extracted in each group.

Bleeding after 15 min was present among 14 patients of Group 1 (14.0 %), 17 patients of Group 2 (17.0 %) and 3 patients of Group 3 (3.0 %); bleeding after 30 min i.e., prolonged immediate post-operative bleeding was present among nine patients of Group 1 (9.0 %) and 15 patients of Group 2 (15.0 %) whereas it was not seen in any patient of Group 3. Local pressure pack with gauze was used to control bleeding in required cases and bleeding was re-assessed after another half an hour. Bleeding after 1 h of extraction was present in nine patients of Group 2 (9.0 %) i.e., the group who had discontinued anti-platelet therapy before extraction whereas it was not seen in any other group. In these nine patients who continued to bleed even after pressure packing of 1 h, gelatin sponge was packed into the extraction socket and patient was asked to bite on

gauze placed over it. Hemostasis was achieved within further half an hour in all nine patients and they were discharged uneventfully.

Statistical analysis revealed significant difference among the three groups with regard to bleeding after 15, 30 min and 1 h with a p value of 0.004, 0.000 and 0.000 respectively.

None of the patients in any group reported with bleeding after 24, 48 h and 1 week. Hence, there were no episodes of late or very late bleeding requiring additional hemostatic measures. Figure 1 shows the evidence of bleeding at different time intervals.

Among nine patients of Group 1 who presented with prolonged immediate post-operative bleeding, three of them were on monotherapy and six of them were on dual therapy and among 15 patients of Group 2, 6 of them were on mono-therapy and 9 of them were on dual therapy. Hence, in both the groups, prolonged immediate post-operative bleeding was more in patients on dual anti-platelet therapy when compared to patients on mono-therapy.

Discussion

Aspirin and clopidogrel are used either as individual drugs in the form of monotherapy or as combination drug in dual therapy. Combining both the drugs provides significant benefit in the prevention of thromboembolic disorders, but at the same time it is also thought to carry a significant risk of bleeding thus demanding an increased consideration while treating such patients. Aspirin is a NSAID that acts by irreversibly inhibiting the enzyme COX-1 for the life of platelet [4] thus reducing the level of platelet stimulant TXA₂ whereas clopidogrel specifically and irreversibly inhibits the P2Y₁₂ subtype of ADP receptor found on platelet cell membranes which is important for aggregation of platelets [5]. Aspirin has anti-platelet, analgesic and anti-inflammatory effects based on the dose. Anti-platelet effect of aspirin is elicited at a low dose of 0.5–1.5 mg/kg body weight/day whereas analgesic and anti-inflammatory effects are present at the doses of 5–10 mg/kg body weight/day and more than 30 mg/kg body weight/day respectively. Therefore, aspirin is effective as anti-platelet drug at much lower doses than that required for analgesic and anti-inflammatory functions. It has been suggested that higher doses develop a dose-dependent inhibition of PGI₂,

Table 1 Type of therapy

Type of therapy	Group		Total
	1	2	
Monotherapy	60 (60.0 %)	71 (71.0 %)	131 (65.5 %)
Dual therapy	40 (40.0 %)	29 (29.0 %)	69 (34.5 %)

Table 2 Number of teeth extracted in each group

Number of teeth extracted	Group			Total
	1	2	3	
<3	92 (92.0 %)	94 (94.0 %)	100 (100 %)	286 (95.3 %)
>3	8 (8.0 %)	6 (6.0 %)	0 (0.0 %)	14 (4.7 %)

Fig. 1 Evidence of bleeding among the three groups at different time intervals

which could be responsible for an increase in thrombotic events.

The decision to stop or continue anti-platelet therapy during dental procedures has always been a dilemma and is been frequently based on certain basic laboratory tests such as bleeding time (BT). Over the years, cutaneous BT has been commonly suggested as a reasonable measure of bleeding risk before doing dental extractions in patients under anti-platelet therapy. However, there have been considerable controversies regarding the relationship of cutaneous BT and the oral bleeding following dental extractions. We did not find any statistically significant difference among the three groups in terms of bleeding time ($p < 0.204$) and it remained within normal limits even when the patients received anti-platelet therapy which was similar to the results of a study done by Adrekian et al. [6] and Verma et al. [7]. Therefore, a correlation between cutaneous BT and the rate of post extraction bleeding cannot be established. Our findings are in accordance with the findings of a study done by Brennan et al. [8] in 36 patients and Brennan et al. [9] in 30 patients. Although more expensive options such as platelet aggregation (impedance) test, platelet function analyzer (PFA 100), and flow cytometry are available, the predictive power of these tests in patients on anti-platelet therapy for bleeding during or after dental procedures is not well documented. The easy availability of Bleeding Time test was the reason for its use in our study.

Though past few decades has witnessed an increase in the number of patients using anti-platelet therapy and requiring dental extractions, considerable controversies still exist regarding management of such patients. Few clinicians recommend continuation of the therapy while others recommend cessation of the therapy for a period ranging from 48 h to 10 days.

The American College of Chest Physicians (ACCP) suggests discontinuing aspirin 7–10 days prior to surgery [10]. However, 48 h after stopping aspirin, up to 20 % of the platelet pool contains non-acetylated cyclooxygenase and TXA_2 released from these platelets can stimulate other platelets unable to produce their own thus restoring the defect in primary hemostasis [11]. Complete recovery of platelet aggregation may occur in 50 % of patients by day 3 and in 80 % of patients by day 4 [12]. Hence, aspirin discontinuation, if required, may be minimized to 3–5 days as opposed to ACCP recommendations of 7–10 days. Though various studies have been done stating varying time periods for cessation of anti-platelet therapy prior to surgical procedures, the implications of interrupting anti-platelet therapy should always be beared in mind when managing these patients. Patients with a history of cerebrovascular or cardiovascular disease in primary care who stop taking low dose aspirin are at a significantly increased risk of non fatal myocardial infarction compared with those who continue the treatment [13].

However, if the discontinuation of anti-platelet agent is associated with certain risk, its continuation may also lead to certain problems such as the risk of bleeding during surgical procedures. Various studies have been done to evaluate the risk of bleeding during major/minor surgical procedures including simple dental extractions.

The post-operative bleeding, relating to dental extractions can be classified into immediate, late and very late [14]. Prolonged immediate post-operative bleeding is defined as bleeding that continues inspite of the pressure pack given for 30 min post-surgery [14–16]. Late bleeding is considered to be clinically significant if it extends beyond 12 h or makes the patient call or return to the surgeon or emergency department or results in hematoma

or ecchymosis within the oral soft tissues or which requires blood transfusion [7, 14, 16, 17]. Very late bleeding is considered present if oozing continues at 24 and 48 h [14].

In our study, bleeding that extended beyond the socket within 1 min of removing the gauze from the operative site was considered as a positive finding for bleeding at that time period. This method was adopted and modified from the procedure of measuring oral bleeding time described by Brennan [9]. It was observed that 9.0 % of patients from Group 1 and 15.0 % of patients from Group 2 had prolonged immediate post-extraction bleeding, the difference being statistically significant ($p = 0.000$). However, none of the patients in any group presented with late and very late post-operative bleeding. This finding is in accordance with the findings of other studies [5–7, 16, 18–20].

We found the incidence of prolonged immediate post-operative bleeding to be higher in patients on dual anti-platelet therapy when compared to patients on monotherapy which is similar to the findings of Girotra et al. [15] and Theodoros et al. [17].

Single or multiple tooth extractions (>3 tooth at a time) were performed. In all the patients of Group 1 and Group 2 who presented with prolonged immediate bleeding, the number of teeth extracted was <3 whereas there were patients in both Groups 1 and 2 in whom more than three teeth were extracted but prolonged bleeding was not seen. Hence we did not find any correlation between the number of teeth extracted and post-extraction bleeding. This observation is in contrast to results of Cardona-Tortajada et al. [21] who found statistically significant difference between bleeding and number of teeth extracted and concluded that more than three teeth should not be extracted at a time.

It is believed that bleeding is more during dental extraction procedures in patients who are allowed to continue anti-platelet therapy when compared to patients who had stopped anti-platelet therapy prior to extraction but the findings of our study were in contrast to this belief.

We found the incidence of prolonged immediate post-operative bleeding to be higher in stopping group (Group 2) when compared to non-stopping group (Group 1). However, this can be attributed to local factors like periodontal and periapical pathology. Nine patients from Group 2 reported with bleeding even after 1 h which was controlled within half an hour of using gelatin sponge. Three of them presented with periapical pathology, two with periodontal abscess and another four patients had compromised periodontal support with surrounding inflamed gingiva. Hence, apart from continuation or discontinuation of anti-platelet therapy, local factors should also be taken into consideration while assessing intraoperative or post-operative bleeding. Lilis et al. [17] and Shah

et al. [14] also found bleeding complications to be associated mostly with periodontitis.

We therefore conclude that, dental extractions can be performed without the risk of significant post-extraction bleeding in patients on single or dual anti-platelet therapy. Although local factors like periodontal and peri-apical pathology might be responsible for increased post-extraction bleeding, it can always be controlled using local hemostatic measures. Hence, there is no need for interrupting the anti-platelet therapy prior to extractions as its risks clearly outweighs its benefits.

Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

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