



## Efficacy of Platelet Rich Fibrin versus chitosan as a hemostatic agent following dental extraction in patients on antiplatelet therapy



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### ABSTRACT

**Objectives:** The aim of this study is to compare the effectiveness of Platelet Rich Fibrin gel and Chitosan gel dressing in providing hemostasis in patients receiving Oral Antiplatelet Therapy and also to evaluate their surgical healing outcome following dental extractions.

**Methodology:** A total of 60 patients under Oral Antiplatelet Therapy indicated for tooth extraction were included for treatment in the study without altering the oral antiplatelet regimens. Patients were allocated equally in two groups; Group A: where PRF gel was packed into the extraction socket, while Group B: Chitosan hydrogel was packed. Timing of hemostasis was noted for each patient of both the groups. Patients were examined for any pain/secondary bleeding/healing/soft tissue dehiscence/alveolar osteitis in the extraction site on first, third and seventh post-operative days.

**Results:** All extraction sockets with Platelet-rich fibrin achieved hemostasis in 2.64 min and sockets with Chitosan hydrogel achieved hemostasis in 1.182 min ( $p < 0.001$ ). Post-operative pain in Group A sites (3.2, 1.4, 0.37 on 1st, 3rd & 7th day respectively) was significantly lower than the control sites (3.4, 1.67, 0.53 on 1st, 3rd & 7th day respectively) p-value 0.001, 0.001 respectively.

**Conclusion:** In this study, Chitosan hydrogel dressing thus proved to be a superior hemostatic agent compared to PRF gel, that significantly shortens the clotting time following dental extraction in patients under antiplatelet therapy. But, PRF gel has superior wound healing properties than Chitosan with less postoperative pain following minor oral surgical procedures under local anesthesia.

### 1. Introduction

Tooth extraction is a common procedure in every dental office and hemostasis following tooth extraction is very essential to prevent excessive blood loss. Episodes of continuous bleeding is not an uncommon medical complication in patients under oral antiplatelet therapy. Due to this, they have become one of the most challenging to treat for an oral surgeon.<sup>1</sup>

These antiplatelet drugs interfere with normal platelet function by decreasing platelet aggregation during clot formation.<sup>1</sup> Low dose aspirin (75 mg–150mg) and clopidogrel (75 mg–200mg) are the routinely prescribed antiplatelet medications. Combination of aspirin and clopidogrel together is also prescribed as it blocks both the complementary pathways in the platelet aggregation cascade, thus producing a synergistic effect.<sup>2</sup> This dual antiplatelet combination is advised in patients with acute coronary syndrome, in ST-segment elevation, acute myocardial infarction and in patients who have coronary artery

stenosis.<sup>2,3</sup>

Such patients when needing dental extraction, oral surgeons either stop or alter their single or dual antiplatelet medication to avoid uncontrolled bleeding following tooth extraction.<sup>3,4</sup> But on stopping or altering this medication, it puts the patients at increased risk of thromboembolic events such as coronary artery thrombosis, cerebrovascular accidents and myocardial infarction.<sup>2</sup> Hence, to create a baseline in treating such patients, use of International Normalized Ratio (INR) is considered as the gold standard for monitoring patients on antiplatelet therapy, as recommended by the American Heart Association and the British Society for Hematology.<sup>4</sup>

Dental extractions in patients on oral antiplatelet therapy are currently performed when the International Normalized Ratio (INR) remains within the treatment range, and avoiding, whenever possible, any modification to the antiplatelet medication. To minimize the risk of post extraction bleeding in such patients, several protocols are now followed, one of them is use of hemostatic agents.<sup>5</sup> Recently Chitosan is

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undergoing lots of discussion as a local hemostatic agent.

The aim of this study was to compare the effectiveness of Chitosan and Platelet Rich Fibrin dressing in aiding hemostasis after dental extractions in patients receiving Oral Antiplatelet Therapy.

Chitosan, a Food and Drug Administration (FDA) approved material, is a natural, cationic biopolymer derived from chitin. Its deacetylation is performed by chemical hydrolysis under severe alkaline conditions under the influence of chitin deacetylase enzyme.<sup>6</sup> Chitosan used in this study has proven biological activities including promotion of wound healing, hemostatic activity, immunity enhancement, mucoadhesion, eliciting biological responses and antimicrobial activity.<sup>7,8</sup> A study conducted by Sinha N et al.<sup>9</sup> elicited superior action of chitosan based dental sponge in aiding hemostasis in extraction sockets in Indian population.

Platelet-rich fibrin (PRF), obtained from centrifugation of whole blood is already known to promote wound healing, bone regeneration, graft stabilization, wound sealing and hemostasis.<sup>10</sup> PRF provides a strong stimulation to osteoblasts, bone mesenchymal stem cells fibroblasts, keratinocytes, thus is an efficient as osteoconductive filling material during the sinus lift procedures and ridge preservation procedures.<sup>11</sup> The aim of this study was to compare the effectiveness of Platelet Rich Fibrin and Chitosan dressing in aiding hemostasis after dental extractions in patients receiving Oral Antiplatelet Therapy.

## 2. Methodology

A total of 60 extraction sites both in maxillary and mandibular anterior and posterior teeth of patients under antiplatelet regimen which were indicated for extraction were included in the study. Patients having a history of liver disease or coagulopathies and allergic to sea products or with severe medical illness were excluded. It involved both male and female patients. This study was planned after due ethical approval from the Institutional Ethics Committee. Patients selected from the above criteria were evaluated and case history and informed consent was recorded. Subjects were randomly allocated into two groups Group A and Group B with 30 subjects in each group.

- GROUP A- The extraction sockets of each patient was packed with Platelet Rich Fibrin gel
- GROUP B- The extraction sockets of each patient was packed with Chitosan hydrogel

Platelet Rich Fibrin gel was prepared in patients of Group A following routine hematological investigations. 5 ml of blood was drawn from the brachial vein of each patient and was centrifuged at 3000 rpm for 10 min. The centrifuged blood had three layers of which the middle fraction containing the fibrin clot was separated out (Fig. 1a–b).

Lyophilised chitosan hydrogel for the study was procured from Everest Biotech, Bangalore. Chitosan was prepared by alkali hydrolysis of chitin obtained from crustacean of shrimps with 50% caustic and subsequently filtered washed and dried. Chitosan was re-dissolved in 1% acetic acid and precipitated by alkali solution. The precipitate was



Fig. 1. a) Platelet Rich Fibrin matrix present in the middle layer b) Fibrin clot 2mm below lower dividing line of the middle fraction is PRF c) Lyophilized chitosan hydrogel.

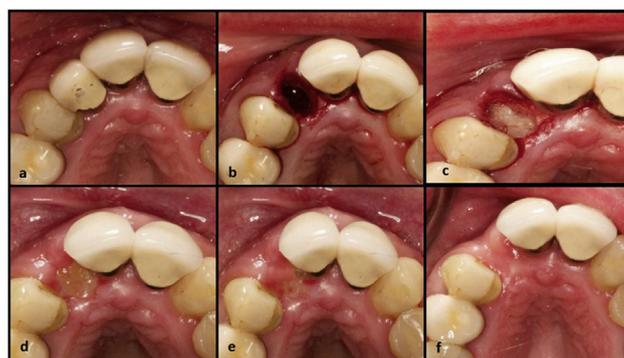


Fig. 2. Procedure in Group A patient- a) 24 indicated for extraction. b) Immediate post extraction. c) Socket with PRF gel. d) 1st post-op day. e) 3rd post-op.

washed and dried. Resultant chitosan has a degree of de-acetylation of about 95–96%. The resultant chitosan flakes were used for preparing the gel for hemostatic properties by mixing 1% Chitosan in 0.8% acetic acid using demineralized water. The gel was kept at 4 deg. C for long stability (Fig. 1).

### 2.1. Surgical procedure

All the dental extractions were performed under local anesthesia using 2% lignocaine containing adrenaline at a concentration of 1:80,000 by standard nerve block techniques. The procedures were performed by the same surgeon and under similar conditions and standard surgical protocol was followed during the entire surgical procedure. Atraumatic extractions of the tooth/teeth were performed.

In Group A subjects, the prepared PRF gel was separated from the red blood cell base. This PRF gel was then placed directly into the post-extraction sockets (Fig. 2).

Whereas in Group B subjects, Chitosan hydrogel filled in 2 ml syringes was placed into the extraction sockets till the height of the alveolar bone (Fig. 3).

Timing of hemostasis, from the placement of the hemostatic agent till the complete cessation of oozing blood from the extraction socket was noted for each patient of both the groups postoperatively using a stopwatch.

Routine Antibiotics and anti-inflammatory drugs were prescribed along with oral hygiene maintenance instructions. Patients were checked for any pain/secondary bleeding/healing/wound break down/soft tissue dehiscence in the extraction site on first, third and seventh post-operative days.

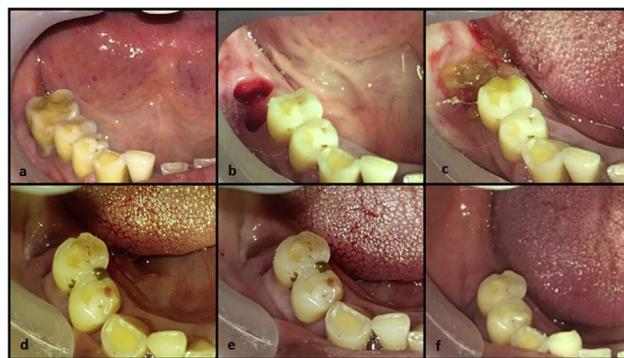


Fig. 3. Procedure in Group B patient a) 46 indicated for extraction b) Immediate post extraction c) Socket with Chitosan hydrogel. d) 1st post-op day. e) 3rd post op day.

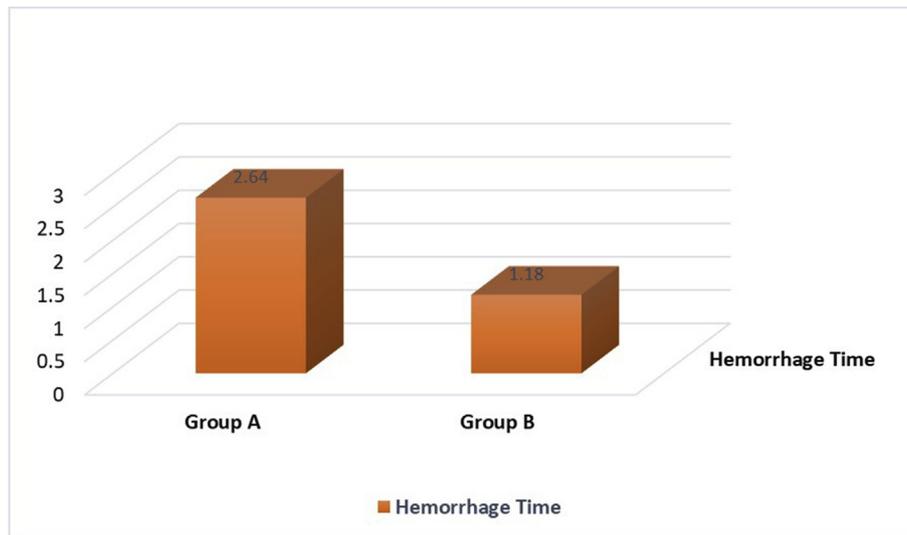


Fig. 4. Correlation of Hemorrhage time in subjects of Group A and Group B.

### 3. Results

Sixty patients were involved in this study, 29 males (48%) and 31 females (52%). Their ages ranged between 35 and 82 years (mean  $58.77 \pm 8.88$  years). All patients were under antiplatelet therapy due to either a prosthetic heart valve, rheumatic heart disease or myocardial infarction. The INR of patients ranged between 1 and 3.5.

#### 3.1. Hemorrhage time

Regarding the time of hemostasis, there was a high statistical significance ( $p < 0.001$ ) between both groups; in Group A, the mean time was  $158.4 \pm 0.52$  s (2.64 min) while in Group B, the mean time was  $70.9 \pm 0.38$  s (1.182 min). On comparison between the mean bleeding time between the two groups, Group B was statistically significant with the Group A ( $p < 0.001$ ) (Fig. 4).

#### 3.2. Pain score

In Group A, the mean pain score based on the Visual Analog Scale and on the 1st postoperative day it was 3.2 (VAS ranging between 2 and 3), 3rd postoperative day it was 1.4 (VAS ranging between 0 and 3) and after 7 days it was 0.37 (VAS ranging between 0 and 3).

In Group B, mean pain score based on the Visual Analog Scale on the 1st postoperative day was 3.4 (VAS ranging between 2 and 5), on 3rd

postoperative day was 1.67 (VAS ranging between 1 and 3), and after 7 days it was 0.53 (VAS ranging between 0 and 1) (Fig. 5).

#### 3.3. Alveolar osteitis

Total of 4 patients, 2 in each group reported with alveolar osteitis on the 7th day after extraction.

#### 3.4. Secondary hemorrhage

In Group A, mild secondary hemorrhage was noted in 2 patients 24 h postoperatively which was successfully managed with sutures. Whereas 4 patients of Group B showed mild secondary bleeding from the extraction sockets which had to be managed with sutures.

#### 3.5. Healing

There was statistically significant ( $p < 0.001$ ) better healing at the Group A extraction sites. 80% of the patients of Group A, showed healthy healing (score of 5) of the extraction sockets based on the custom-made evaluation chart by 7th postoperative day. In the case of Group B, only 60% of the patients showed healthy healing (score of 5) till the 7th postoperative day.

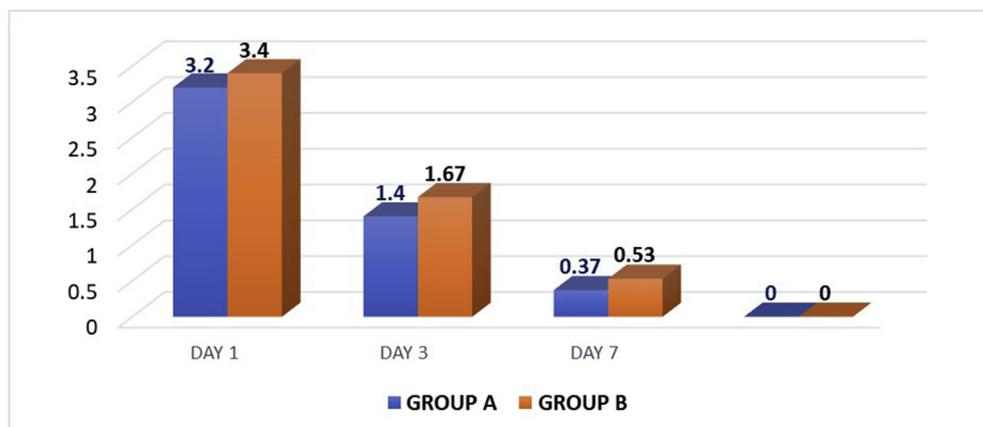


Fig. 5. Correlation of Mean Pain Score in subjects of Group A and Group B on 1st, 3rd and 7th postoperative day.

#### 4. Discussion

Oral antiplatelet drugs, such as aspirin and clopidogrel, irreversibly inhibit platelet aggregation and this lasts for the life of the platelets (7–10 days), leading to increased bleeding tendency and increase in INR values in such patients.<sup>3</sup>

Therefore, CAPRIE Steering Committee in their study recommended that INR should not be higher than 4.0, if patient is to be taken for dental procedures who is under antiplatelet drugs.<sup>12</sup>

In the present study, Chitosan hydrogel and Platelet Rich Fibrin were used to control bleeding for extraction wound in patients on Oral antiplatelet therapy. We achieved hemostasis with Chitosan Hydrogel in a shorter mean time of 1.18 min, compared to Platelet rich fibrin sites which took 2.64 min, thus demonstrating the effectiveness of using Chitosan hydrogel dressing in patients on antiplatelet drugs.

The shorter hemostasis time taken by Chitosan hydrogel can be explained by its electropositive nature which reacts with electro-negative red blood cells and hence the clot formation is based on electrostatic charge attraction and not by the quantity and quality of clotting factors.<sup>13,14</sup>

Since Chitosan hydrogel doesn't require the intrinsic or extrinsic clotting pathways to achieve hemostasis, the hemophilic patient can also be locally treated in the similar manner.<sup>15</sup>

During PRF preparation, leucocytes in the collected blood tends to secrete cytokines as a response to the artificially induced inflammatory phenomena during centrifugation.<sup>16</sup> This theory could be a probable reason for reduction of postoperative infections and enhanced healing when PRF is used as a postsurgical additive.<sup>10</sup>

The present study also gave improved post-operative healing of extraction sites in both the groups yet Platelet Rich Fibrin gave superior results. This might be because Platelet Rich Fibrin acts as an autogenous source of multiple growth factors i.e. PDGF, VEGF etc.<sup>14</sup>

Shen et al.<sup>17</sup> in one of their study, showed release of growth factors from human platelets induced by the use of Chitosan, which may help explain our positive findings corresponding to wound healing in Group B. Cunha-Reis et al.<sup>18</sup> reported that cell adhesion is consistent with the nature of Chitosan dental dressing used in this study.

Additionally, it was also found that patients who were treated with the PRF showed minimal pain and accelerated healing when evaluated on subsequent follow ups, while those treated with the Chitosan hydrogel showed transient elevation in pain scores on the first few post-extractions days.

The persistent moderate pain for few days in Chitosan packed extraction sites might be due to the small amount of unreacted residual acetic acid produced and remnants of Chitosan.<sup>19</sup> Foreign materials packed in the recent extraction sockets tends to disturb the normal healing mechanism, while PRF, due to its autogenic nature, is completely tolerated.<sup>20</sup> Incidence of alveolar osteitis was in significant as both the groups.

On the basis of this study, the hypothesis that Chitosan hydrogel is an excellent new generation hemostatic agent that significantly shortens the hemorrhage time following dental extraction in patients on Oral antiplatelet therapy, is hence verified.

Still the hemostatic properties of the Chitosan hydrogel dressing do not obviate the need for thorough pre/post-operative evaluation including patient's INR status. All patients in this study were treated without altering their antiplatelet medication regimens, based on the evidence that the benefit of preventing thromboembolism outweighs the risk of bleeding.

#### 5. Conclusion & summary

From the analysis of this study, it can be concluded that for dental extractions of patients on oral antiplatelet therapy, discontinuing/altering their regimen is not recommended as there is an increased risk of thromboembolism. Extraction can be carried out safely with the use of

local hemostatic agents like Chitosan hydrogel. Chitosan proved to be a superior hemostatic agent compared to PRF gel, that significantly shortens the hemostasis time following dental extraction: 1.18 min and also possess good wound healing properties. Although PRF also possess significant hemostatic action, however long-term studies with greater sample size is needed for further conclusive results.

It is essential to evaluate the risks of intraoperative and post-operative hemorrhage, and also the extent of surgical trauma to be subjected in order to establish an effective protocol. Therefore, it is advised that performing a surgical procedure as atraumatic as possible, use of effective local hemostatic agents and patient's sincerity towards postoperative instructions are the key points to be considered in all the patients on antiplatelet therapy. This research may also be directed in determining further utility of Chitosan in the field of Oral and Maxillofacial Surgery.

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#### References

- Aframian DJ, Lalla R, Peterson D. Management of dental patients taking common hemostasis altering medications. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(suppl 1) S45.e1-S45.e11.
- Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg.* 2005 Sep;63(9):1262–1265.
- Madhulaxmi M, Abdul Wahab PU. Can aspirin be continued during dental extraction? *Int J Pharm Pharm Sci.* 2014;6(1):20–23.
- Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg.* 2005 Sep;63(9):1262–1265.
- Sammartino G, Ehrenfest DMD, CarileF, Tia M, Bucci P. Prevention of hemorrhagic complications after dental extractions into open heart surgery patients under anticoagulant therapy: the use of leukocyte- and platelet-rich fibrin. *J Oral Implantol.* 2011;37(6):681–690.
- Pogorielov M, Vitalii ZS. Chitosan as a hemostatic agent: current state. *Eur J Med.* 2015;2:24–33.
- Ezoddini-Ardakani F, Navab Azam A, Yassaei S, Fatehi F, Rouhi G. Effects of chitosan on dental bone repair. *Health.* 2011;2011:200–205.
- Burkatovskaya M, Tegosa JP, Swietlika E, Demidovaa T, Castanoa AP, Hamblina MR. Use of chitosan bandage to prevent fatal infections developing from highly contaminated wounds in mice. *Biomaterials.* 2006;27:4157–5164.
- Sinha N, Mazumdar A, Mitra J, Sinha G, Baunthiyal S, Baunthiyal S. Chitosan based axiostat dental dressing following extraction in cardiac patients under antiplatelet therapy. *Int J Oral Health Med Res.* 2017;3(5):65–67.
- Harfoush M, Boutros E, Nashar A. Evaluation of topical application of platelet rich fibrin (PRF) in homeostasis of the bleeding after teeth extraction in patients taking warfarin. *Int Den J Stu Res.* 2016;4(3):144–147.
- Gürbüz B, Pikköken L, Tunali M, Urhan M, Küçükodaci Z, Ercan F. Scintigraphic evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. *J Oral Maxillofac Surg.* 2010;68:980–989.
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 1996;348(9038):1329–1339.
- Malmquist JP, Clemens SC, Hal J, Oien HJ, Wilson SL. Hemostasis of oral surgery wounds with the HemCon dental dressing. *J Oral Maxillofac Surg.* 2008;66:1177–1183.
- Ming K, Guang X, Xing K, Park HJ. Antimicrobial properties of chitosan and mode of action: a state of the art review. *Int J Food Microb.* 2010;144:51–63.
- Ezoddini-Ardakani F, Navab Azam A, Yassaei S, Fatehi F, Rouhi G. Effects of chitosan on dental bone repair. *Health.* 2011;3:200–205.
- Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part II: platelet-related biologic features. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101:e45–50.
- Shen EC, Chou TC, Gau CH, Tu HP, Chen YT, Fu E. Releasing growth factors from activated human platelets after chitosan stimulation: a possible bio-material for platelet-rich plasma preparation. *Clin Oral Implant Res.* 2006;17(5):572–578.
- Cunha-Reis C, Tuzlakoglu K, Baas E, Yang Y, El Haj A, Reis RL. Influence of porosity and fibre diameter on the degradation of chitosan fibre-mesh scaffolds and cell adhesion. *J Mater Sci Mater Med.* 2007;18:195–200.
- Kale TP Singh AK, Kotrashetti SM, Kapoor A. Effectiveness of hemcon dental dressing versus conventional method of haemostasis in 40 patients on oral antiplatelet drugs. *Sultan Qaboos Univ Med J.* 2012;12(3):330–335.
- Naik Balaram, Karunakar P, Jayadev M, Marshal V Rahul. Role of Platelet rich fibrin in wound healing: a critical review. *J Conserv Dent.* 2013;16(4):284–293.