Clinical Study
Postoperative Bleeding Risk for Oral Surgery under Continued Clopidogrel Antiplatelet Therapy

Alexander Gröbe,1 Meike Fraederich,1 Ralf Smeets,1 Max Heiland,1 Lan Kluwe,1 Jürgen Zeuch,2 Martina Haase,2 Johannes Wikner,1 Henning Hanken,1 Jan Semmusch,1 Ahmed Al-Dam,1 and Wolfgang Eichhorn1,2
1Department of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany
2Department of Oral and Maxillofacial Surgery, General Hospital Balingen, Tuebinger Straße 30, 72336 Balingen, Germany

Correspondence should be addressed to Wolfgang Eichhorn; w.eichhorn@uke.de

Received 20 July 2014; Revised 8 October 2014; Accepted 22 October 2014

Academic Editor: Betti Giusti

Copyright © 2015 Alexander Gröbe et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Object. To determine the incidence of postoperative bleeding for oral osteotomy carried out under continued monoantiplatelet therapy with clopidogrel and dual therapy with clopidogrel/aspirin. Design. Retrospective single center observatory study of two study groups and a control group. Methods. A total of 64 and 60 oral osteotomy procedures carried out under continued monoclopidogrel therapy and dual clopidogrel/aspirin therapy, respectively, were followed for two weeks for postoperative bleeding. Another 281 similar procedures were also followed as a control group. All oral osteotomy procedures were carried out on an outpatient basis. Results. We observed postoperative bleeding in 2/281 (0.7%) cases in the control group, in 1/64 (1.6%) cases in the clopidogrel group, and in 2/60 (3.3%) cases in the dual clopidogrel/aspirin group. The corresponding 95% confidence intervals are 0–1.7%, 0–4.7%, and 0–7.8%, respectively, and the incidences did not differ significantly among the three groups (P > 0.09). Postoperative hemorrhage was treated successfully in all cases with local measures. No changes of antiplatelet medication, transfusion, nor hospitalisation were necessary. No major cardiovascular events were recorded. Conclusions. Our results indicate that minor oral surgery can be performed safely under continued monoantiplatelet medication with clopidogrel or dual antiplatelet medication with clopidogrel/aspirin.

1. Introduction
Clopidogrel is a common antiplatelet agent used as an alternative for aspirin or in dual antiplatelet therapy with aspirin [1–3]. Clopidogrel irreversibly inhibits adenosine diphosphate, which is necessary for platelet aggregation while aspirin works through inactivation of the enzyme cyclooxygenase. Both drugs prevent clot formation for the lifetime of the platelet, which is 9–11 days [4, 5].

When patients under such antiplatelet therapy need surgery, the surgeon is confronted with the choice of interrupting the 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 surgery [3, 6, 7]. However, a perioperative interruption of antiplatelet medication is still frequently practiced for dental procedures [8]. In particular, clopidogrel, either for single or dual therapy, is feared for exposing patients to a high risk of bleeding [9] since it takes 5–10 days for full recovery of platelet activity after withdrawal.

The purpose of this study is to evaluate the postoperative bleeding rate for oral osteotomy and other invasive oral procedures under continued monoclopidogrel therapy or dual clopidogrel/aspirin therapy. We focus on oral osteotomy because this procedure involves invading the bone and
therefore has a higher bleeding risk than other minor oral procedures such as tooth extraction.

2. Materials and Methods

A total of 405 oral osteotomy procedures were followed for 2 weeks. Some patients underwent multiple procedures. Each procedure was counted as an independent case (not the number of the patients) and subsequent analysis was based on this definition. A total of 64 procedures were carried out in patients who were under monotherapy with clopidogrel (75 mg/day) and another 60 procedures in patients under dual antiplatelet treatment with clopidogrel (75 mg/day) and aspirin (100 mg/day). In all these 124 cases, medication was continued as usual and no change, neither interruption, reduction, nor bridging, was conducted. The rest of 281 osteotomy procedures were carried out in patients who were not under any anticoagulation or antiplatelet treatment.

All procedures were carried out by the senior author himself under local anaesthesia with articaine 4% and epinephrine 1:200.000 (Ultracaine D-S, Sanofi-Aventis) on an outpatient basis. In case of contraindications to epinephrine, scandicain 4% (Scandicain 4%, AstraZeneca) was used. After osteotomy, meticulous curettage of the extraction socket was performed and all of granulation tissue removed. Local hemostasis was achieved with a collagen fleece; wound closure was carried out with sutures and an acrylic splint. All patients received a single shot of 1000 mg amoxycillin as a prophylactic antibiotic measure. Postoperative pain was treated with ibuprofen 400 mg every 6 hours for 3 days or further if needed. Patients were routinely seen on the first, third, seventh, tenth, and 14th day. A bleeding was defined as an event that required additional surgical intervention.

Patient data were recorded using Evident (Evident, Bingen, Germany) and evaluated using SPSS. Confidence interval for bleeding incidence was calculated for 95% level [10].

3. Results

Postoperative bleeding was generally rare. Among the 281 osteotomy procedures for patients not under any antiplatelet medication, bleeding occurred only in 2 (0.7%) cases with a 95% confidence interval of 0.2–2.6%. For the 64 and 60 procedures under continued mono- and dual antiplatelet therapy, postoperative bleeding occurred in 1 (1.6%) and 2 (3.3%) cases, with 95% confidence intervals of 0.3–8.3% and 0.9–11.3%, respectively. The bleeding rates were not significantly higher in the mono- and dual antiplatelet treatment groups compared to that in the group of nonanticoagulation (Table I). However, the statistical powers were only 0.18 and 0.45.

All bleedings occurred within 48 hours after the operation. For 4 out of the 5 bleeding cases, local measures with pressure on the osteotomy wound with methylcellulose was sufficient to achieve hemostasis. For the last case, fibrin glue (Tissucol Duo S, Baxter) was applied in addition to the methylcellulose. No change of the antiplatelet medication, no transfusion of blood, nor hospital admittance was necessary.

4. Discussion

The postoperative bleeding rate for osteotomy in the present study was generally low and was only slightly increased for cases under continued mono- and dual clopidogrel therapies

---

### Table 1: Clinical features and bleeding rates in control and antiplatelet groups.

| Features and Parameters | Antiplatelet medication | Chi-test, t-test (control versus mono-/dual therapy group) |
|-------------------------|-------------------------|----------------------------------------------------------|
|                         | Control | Clopidogrel | Clopidogrel/Aspirin | Significance P | Power |
| Number of cases         |         | 281        | 64                 | 60              |       |
| Postoperative bleeding  |         |            |                    |                |       |
| Case                    | 2       | 1          | 2                  |                |       |
| Rate (95% confidence)   | 0.7%    | 1.6%       | 3.3%               | 0.46/0.14      | 0.18/0.45 |
| Age (years)             | 60.7 ± 6.3 | 67.9 ± 14.6 | 64.0 ± 10.8       | <0.00/<0.00    | 0.98/0.74 |
| Male/female             | 129/152 | 35/29      | 44/16              |                | 0.21/0.00 | 0.24/0.98 |
| Numbers of teeth        | 1.7 ± 1.8 | 1.5 ± 0.8  | 1.5 ± 1.1         | 0.32/0.38      | 0.39/0.30 |
| Dose                    | 75 mg/day | 75 mg + 100 mg/day |
| Indication for antithrombotic medication |         |            |                    |                |       |
| Apoplexy + TIA          | 6       | 7          |                    |                |       |
| Stent + bypass          | 16      | 28         |                    |                |       |
| Myocardial infarction + other heart disorders | 12 | 13 | 0.15 |
| Others                  | 3       | 3          |                    |                |       |
| Unknown                 | 27      | 9          |                    |                |       |
(from 0.7% to 1.6% and 3.3%, resp.). However, due to the small sample size, especially that of the two therapy groups, the statistical powers were extremely low (0.18 and 0.45). The results of the present study are therefore of preliminary nature. Due to the small sample size, the data are not sufficient for detecting small differences in postoperative bleeding rates. At a 95% confidence level, the ranges of the bleeding rates can be estimated as below 8.3% and 11.3% for the mono- and dual therapy cases, respectively. With larger sample size in future studies, we expect to narrow down these ranges.

We have demonstrated that the bleedings were all manageable with simple local measures without stopping or modifying the anticoagulation therapy. This may ease the fear of lacking immediate countermeasures for clopidogrel to some extent [6, 11, 12].

For minor oral surgery such as teeth extraction, increasing data suggests that continuing antiplatelet medication during oral surgery does not increase the bleeding risk notably whereas the role of local hemostasis is emphasized [13, 14]. However, only very limited cases involved clopidogrel [15–17]. For example, Park et al. [18] observed 1.7% (1/59) excessive intraextraction bleeding under continued dual antiplatelet therapy but failed to follow up the patients for subsequent bleeding incidences. Girotra et al. [19] reported 5.2% immediate postoperative bleeding for oral surgery (mostly dental extraction) with continued monoclopidogrel and 7.9% for dual clopidogrel therapies. Oral osteotomy is more invasive than minor oral procedures such as standard teeth extraction. Nevertheless, the postoperative bleeding rates of 1.6% and 3.3% under continued monop- and dual clopidogrel therapy in our study are comparable or even below the already published ones.

We have recently followed bleeding for similar procedures under continued aspirin and phenprocoumon therapy and obtained the rates of 1.6% and 7.4%, respectively. Our findings confirm that the postoperative bleeding rates under continued anticoagulation therapy vary depending on the target of the therapy and the used reagents [20–22]. In case of continued phenprocoumon therapy, surgeons should be more cautious. By contrast, continuing antiplatelet therapy with aspirin and clopidogrel is likely safer.

In any case, preventive measures are recommendable for oral osteotomy under continued antiplatelet therapy. For example, we close the wound using a collagen sponge and sutures and further covered the site with an acrylic splint. Others pointed out possible timing effect and suggested the beginning of the week and morning hours for the surgery [13, 23]. Since most bleeding events are within 2 days after the surgery, a 24-hour hotline for two days may provide an effective measure ensuring quick response in case of bleeding.

5. Conclusion

Our results suggest that, despite its more invasive nature, oral osteotomy can be performed safely under continued monoantiplatelet medication with clopidogrel or dual antiplatelet medication with clopidogrel/aspirin.

Conflict of Interests

The authors declare they have no conflict of interests.

Authors’ Contribution

Alexander Gröbe and Meike Fraederich contributed equally to this paper.

References

[1] A. M. Al-Harkan and G. A. Al-Ayoub, “Should antiplatelet and anticoagulant medications be discontinued before minor oral surgery procedures?” Journal of the Canadian Dental Association, vol. 78, no. 1, article c24, 2012.
[2] P.-G. Chassot, A. Delabays, and D. R. Spahn, “Perioperative use of anti-platelet drugs,” Best Practice and Research: Clinical Anaesthesiology, vol. 21, no. 2, pp. 241–256, 2007.
[3] N. G. Daniel, J. Goulet, M. Bergeron, R. Paquin, and P.-E. Landry, “Antiplatelet drugs: is there a surgical risk?” Journal of the Canadian Dental Association, vol. 68, no. 11, pp. 683–687, 2002.
[4] J. N. George and S. J. Shattil, “The clinical importance of acquired abnormalities of platelet function,” The New England Journal of Medicine, vol. 324, no. 1, pp. 27–39, 1991.
[5] J. R. Vane, E. E. Anggard, and R. M. Botting, “Regulatory functions of the vascular endothelium,” The New England Journal of Medicine, vol. 323, no. 1, pp. 27–36, 1990.
[6] E. Aldridge and L. L. Cunningham Jr., “Current thoughts on treatment of patients receiving anticoagulation therapy,” Journal of Oral and Maxillofacial Surgery, vol. 68, no. 11, pp. 2879–2887, 2010.
[7] J. W. Little, C. S. Miller, R. G. Henry, and B. A. McIntosh, “Antithrombotic agents: implications in dentistry,” Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics, vol. 93, no. 5, pp. 544–551, 2002.
[8] R. Rossini, D. Capodanno, C. Lettieri et al., “Prevalence, predictors, and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug eluting stent implantation,” American Journal of Cardiology, vol. 107, no. 2, pp. 186–194, 2011.
[9] J. D. Douketis, A. C. Spyropoulos, F. A. Spencer et al., “Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines,” Chest, vol. 141, no. 2, supplement, pp. e326S–e350S, 2012.
[10] R. G. Newcombe, “Two-sided confidence intervals for the single proportion: comparison of seven methods,” Statistics in Medicine, vol. 17, pp. 857–872, 1998.
[11] T. Kövesi and D. Royston, “Editorial I. Is there a bleeding problem with platelet-active drugs?” British Journal of Anaesthesia, vol. 88, no. 2, pp. 159–163, 2002.
[12] G. Born and C. Patrono, “Antiplatelet drugs,” British Journal of Pharmacology, vol. 147, no. 1, pp. S241–S251, 2006.
[13] M. Pototski and J. M. Amenábar, “Dental management of patients receiving anticoagulation or antiplatelet treatment,” Journal of Oral Science, vol. 49, no. 4, pp. 253–258, 2007.
[14] J. J. Napeñas, F. C. D. Oost, A. Degroot et al., “Review of postoperative bleeding risk in dental patients on antiplatelet therapy,” Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, vol. 115, no. 4, pp. 491–499, 2013.
[15] C. G. Partridge, J. H. Campbell, and F. Alvarado, “The effect of platelet-altering medications on bleeding from minor oral surgery procedures,” Journal of Oral and Maxillofacial Surgery, vol. 66, no. 1, pp. 93–97, 2008.

[16] F. Cardona-Tortajada, E. Sainz-Gómez, J. Figuerido-Garmendia et al., “Dental extractions in patients on antiplatelet therapy. A study conducted by the Oral Health Department of the Navarre Health Service (Spain),” Medicina Oral Patologia Oral Y Cirugia Bucal, vol. 14, no. 11, pp. e588–e592, 2009.

[17] A. Cañigrall, F.-J. Silvestre, G. Cañigrall, M. Alós, A. Garcia-Herraiz, and A. Plaza, “Evaluation of bleeding risk and measurement methods in dental patients,” Medicina Oral, Patologia Oral y Cirugia Bucal, vol. 15, no. 6, pp. e863–e868, 2010.

[18] M.-W. Park, S.-H. Her, J. B. Kwon et al., “Safety of dental extractions in coronary drug-eluting stenting patients without stopping multiple antiplatelet agents,” Clinical Cardiology, vol. 35, no. 4, pp. 225–230, 2012.

[19] C. Girotra, M. Padhye, G. Mandlik et al., “Assessment of the risk of haemorrhage and its control following minor oral surgical procedures in patients on anti-platelet therapy: a prospective study,” International Journal of Oral and Maxillofacial Surgery, vol. 43, no. 1, pp. 99–106, 2014.

[20] W. Eichhorn, J. Burkert, O. Vorwig et al., “Bleeding incidence after oral surgery with continued oral anticoagulation,” Clinical Oral Investigations, vol. 16, no. 5, pp. 1371–1376, 2012.

[21] W. Eichhorn, L. Kluwe, M. Heiland, and A. Gröbe, “Lack of evidence for increased risk of postoperative bleeding after cutaneous surgery in the head and neck in patients taking aspirin,” British Journal of Oral and Maxillofacial Surgery, vol. 52, no. 6, pp. 527–529, 2014.

[22] H. Hanken, F. Tieck, L. Kluwe et al., “Lack of evidence for increased postoperative bleeding risk for dental osteotomy with continued aspirin therapy,” Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. In press.

[23] C. Scully and A. Wolff, “Oral surgery in patients on anticoagulant therapy,” Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, vol. 94, no. 1, pp. 57–64, 2002.