Prevention of Hemorrhagic Complications After Dental Extractions Into Open Heart Surgery Patients Under Anticoagulant Therapy: The Use of Leukocyte- and Platelet-Rich Fibrin

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1 Leukocyte- and platelet-rich fibrin (L-PRF) is a biomaterial commonly used in periodontology and implant dentistry to improve healing and tissue regeneration, particularly as filling material in alveolar sockets to regenerate bone for optimal dental implant placement. The objective of this work was to evaluate the use of L-PRF as a safe filling and hemostatic material after dental extractions (or avulsions) for the prevention of hemorrhagic complications in heart surgery patients without modification of the anticoagulant oral therapy. Fifty heart surgery patients under oral anticoagulant therapy who needed dental extractions were selected for the study. Patients were treated with L-PRF clots placed into 168 postextraction sockets without modification of anticoagulant therapy (mean international normalized ratio = 3.16 ± 0.39). Only 2 patients reported hemorrhagic complications (4%), all of which resolved a few hours after the surgery by compression and hemostatic topical agents. Ten patients (20%) showed mild bleeding, which spontaneously resolved or was resolved by minimal compression less than 2 hours after surgery. No case of delayed bleeding was reported. The remaining 38 patients (76%) showed an adequate hemostasis after the dental extractions. In all cases, no alveolitis or painful events were reported, soft tissue healing was quick, and wound closure was always complete at the time of suture removal one week after surgery. The proposed protocol is a reliable therapeutic option to avoid significant bleeding after dental extractions without the suspension of the continuous oral anticoagulant therapy in heart surgery patients. Other applications of the hemostatic and healing properties of L-PRF should be investigated in oral implantology.

Key Words: platelet-rich fibrin, heart surgery patient, anticoagulant therapy, hemorrhagic complications, dental avulsion, dental extraction

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Dental extractions in heart surgery patients treated with artificial mechanical heart valves under anticoagulant oral therapy (warfarin) can be difficult as these patients present a significant risk for postoperative hemorrhagic complications.[1] Currently, many authors do not recommend suspending the anticoagulant therapy and replacing it with heparin before a minor surgery to avoid serious thromboembolic complications.[2,3] To control the hemorrhagic risk in patients under anticoagulant therapy, several protocols have been proposed in the literature. Some authors have recommended a combination of local antifibrinolytic therapy and hemostatic agents for the prevention of postoperative bleeding due to oral surgery.[4] Other authors have suggested that many patients can safely undergo outpatient oral surgical procedures without changes in their regular therapeutic anticoagulant regimen and without additional medical interventions, or by using the tranexamic acid as an antifibrinolytic local agent for 2 days after the surgery.[5–7] Other protocols have recommended protecting the alveolar extraction sockets with oxide cellulose and fibrin glue in association with tranexamic acid rinses after the surgery.[8,9] Other authors have proposed the sole use of fibrin glue to prevent the hemorrhagic complications, but these fibrin products are expensive and raise the question of the potential for infectious contaminations.[10,11]

Recently, the use of platelet-rich plasma (PRP) gel in postextraction sockets, with no significant modification of anticoagulant oral therapy, showed good results for preventing postoperative bleeding in patients taking anticoagulants.[12] The objectives of the PRP technologies are to gather the platelets from an anticoagulated blood harvest and to reinject these platelet suspensions into a damaged site to promote healing through the massive release of platelet growth factors. In most oral applications, the PRP suspension is activated with bovine thrombin (or an equivalent activator) to form a light fibrin gel (which is easier to use in clinical applications, similar to a fibrin glue). Many platelet concentrates are expensive, however, and take quite a long time to prepare, so their daily use remains difficult.[13] Yet, many different products have been developed in this field,[13] and some PRP gel techniques are efficient and inexpensive.[14,15]

Platelet-rich fibrin (PRF) belongs to another family of platelet concentrates (with a denser fibrin architecture than the PRP gels and a different cell/factor/matrix organization)[13,16] where the objective is to obtain a dense autologous platelet-fibrin gel without the use of anticoagulant and activator. The PRF procedure was developed and perfected by Choukroun et al[17] and Dohan et al[18] and is commonly classified as a leukocyte- and platelet-rich fibrin (L-PRF) biomaterial.[13,16] This technique is simple and inexpensive: blood is collected in tubes without anticoagulant and is immediately centrifuged for 12 minutes. Three layers appear in the tube: a red blood cell base at the bottom, acellular plasma at the top, and a strong PRF clot in the middle. The healing properties of this material are related to its dense fibrin scaffold[19] and its platelet and leukocyte content.[20–22] The PRF shows a strong stimulation of most oral cell lineages in vitro (osteoblasts, fibroblasts, keratinocytes, bone mesenchymal stem cells)[23,24] and is currently used to improve soft tissue healing and bone remodeling in oral[25,26] and maxillofacial surgery, particularly in oral implantology[27–29] and ear, nose, and throat surgery.[30–32] The PRF seems particularly efficient as osteoconductive filling material during the sinus-lift procedure.[33] However, in order to define relevant clinical applications, PRF has to be used as a fibrin-based living biomaterial, and not only as a source of growth factors.[34]

PRF is particularly useful in daily practice as filling material for regenerating alveolar

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sockets in order to place modern dental implants[35] in regenerated bone ridges. This approach is particularly interesting in more complex situations, such as in patients with general pathologies associated with delayed healing or coagulation. The aim of this research, therefore, was to evaluate the use of PRF as an easy and safe filling and hemostatic biomaterial in the prevention of hemorrhagic complications after dental extractions (or avulsions)[36] in heart surgery patients without modification of the anticoagulant oral therapy.

Materials and Methods

From January 2005 to January 2008 at the Oral Surgery Department of the University of Naples Federico II, 50 heart surgery patients (28 women and 22 men) were selected for the study. All patients were nonsmokers, aged 47 to 67 years. They had a mechanical heart valve substitution (21 with mitral valve substitution and 29 with aortic valve substitution) and followed an anticoagulant oral therapy with warfarin (all with Coumadin 5 mg, 1 tablet per day in 24 patients and 1.5 tablet per day in 26 patients). Evaluated by standard laboratory method, the mean international normalized ratio (INR) value was 3.16 $\pm$ 0.39. All selected patients were in an equilibrated cardiac condition and were only treated by anticoagulant therapy; they were taking no other cardiac medications.

All patients were informed about the characteristics and the objectives of the study and signed an informed consent disclosure form that had been reviewed and approved by the Committees for the Protection of Human Subjects and Scientific Review. This study and the patient's informed consent form were approved by the University of Naples Federico II Institutional Review Board.

After a local anesthesia without vasoconstrictor agents, the patients underwent single or multiple extractions for a total of 168 teeth. No patient underwent more than 4 dental extractions at the same time. None of the patients suspended the anticoagulant oral therapy and none of the patients received heparin before the surgical procedure. Gentle luxation and extraction of the teeth were performed to preserve the integrity of the buccal and lingual plates (Figures 1 and 2). In a few cases, the teeth were cut with a diamond burr in 2 fragments to avoid periodontal bone trauma during the extraction.

The PRF was prepared through a single centrifugation of whole blood (PRF production kits, Process, Nice, France) lasting 18 minutes. Blood was collected without anticoagulant from the brachial vein by a nurse 20 minutes before the extractions, according to the protocol for anticoagulated patients (ie, with longer centrifugation time, 18 minutes instead of 12 minutes). Each 9 mL tube produced one PRF clot. The volume of harvested blood was related to the number of dental extractions and the quantity of PRF clots required to fill the alveolar sockets (from 18 mL to 54 mL, or 2 to 6 PRFs).[18] After centrifugation, each PRF clot was separated from the red blood cell base, condensed, modeled on a sterile metal plate (Figure 1A), placed directly into the postextraction sockets, and stabilized by 3/0 silk suture (Figure 2B). All extractions were performed with minimal bone trauma to achieve an adequate support for the PRF gel (Figures 1B and 2A). There was always one PRF clot introduced in each extraction site (Figure 2B).

Each surgical intervention had a maximum duration of 20 minutes to decrease the surgical stress for the patient, and the extraction/curettage part of the surgery always lasted less than 5 minutes. However, the patients remained under the care of the department for several hours after the surgical procedure. Bleeding assessments were performed every 15 minutes for 3 hours after the extractions, and then every hour for

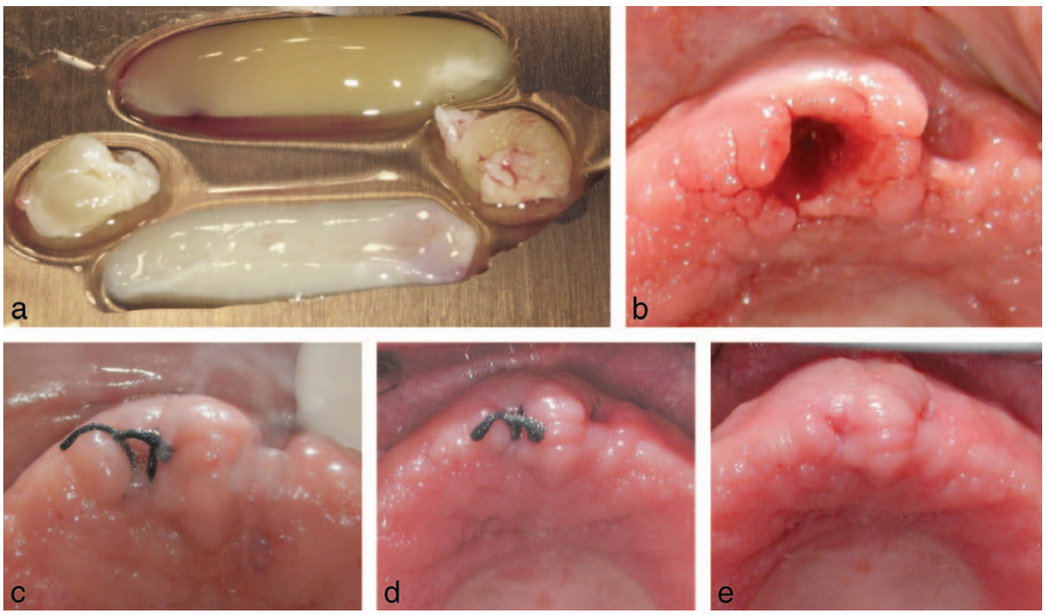

Figure 1. (A) Platelet-rich fibrin (PRF) was prepared with a single centrifugation of whole blood. Using the adequate sterile metal tool (PRF Box, Process, Nice, France), the PRF clot (up) can be modeled into a strong fibrin membrane (down) or condensed PRF clots (lateral) that are easy to insert in compression into the postextraction sockets. (B) A postextraction socket in the anterior maxilla just after extraction in a patient who had undergone open heart surgery and was under anticoagulant therapy. (C) Soft tissue healing 2 days after extraction and filling with a condensed PRF clot. No delayed bleeding occurred. (D) At 7 days after surgery, the extraction socket is completely closed. (E) At 7 days after surgery, after suture removal.

the next 6 hours. This examination reported the subjective evaluation of blood amount on sterile gauze and the bleeding duration.

According to the classification by Souto and colleagues,[5] we defined mild bleeding as bleeding that stopped spontaneously or with minimal local compression, and severe bleeding or major hemorrhagic complication was defined as bleeding that did not stop with previous measures and required continuous local compression using a gauze pack soaked in an antifibrinolytic agent until the bleeding stopped.

Furthermore the postextraction sites were monitored every day after the surgery (Figures 1C, 2C, and 2D) until the suture removal to assess potential late hemorrhagic complications and to evaluate pain and tissue healing. The suture was removed 1 week after the surgery (Figures 1D and 1E).

To prevent infectious endocarditis complications, the patients underwent intramuscular wide-spectrum antibiotic therapy with ceftriaxone (1 g, once a day) and Nebcin (5 mg/kg, twice a day) from 2 days before until 3 days after the surgical procedures. The medications were given at the hospital. All patients followed a soft and liquid diet for 24 hours after the surgery, without mouth rinses over the same period. Oral hygiene (mainly toothbrushing) was suspended for 24 hours after dental extractions.

Results

The proposed protocol achieved satisfactory results, as presented in Tables 1 and 2. Each patient underwent 1 to 4 extractions (mean $= 2.8 \pm 1.2$), for a total of 168 teeth (75 maxillary and 93 mandibular extractions).

There were only 2 hemorrhagic complications (4%); these occurred in 2 patients with an INR of 3.7, a 61-year-old man and a 54-year-old woman. These complications were solved in a few hours by compression with sterile gauzes and the local application

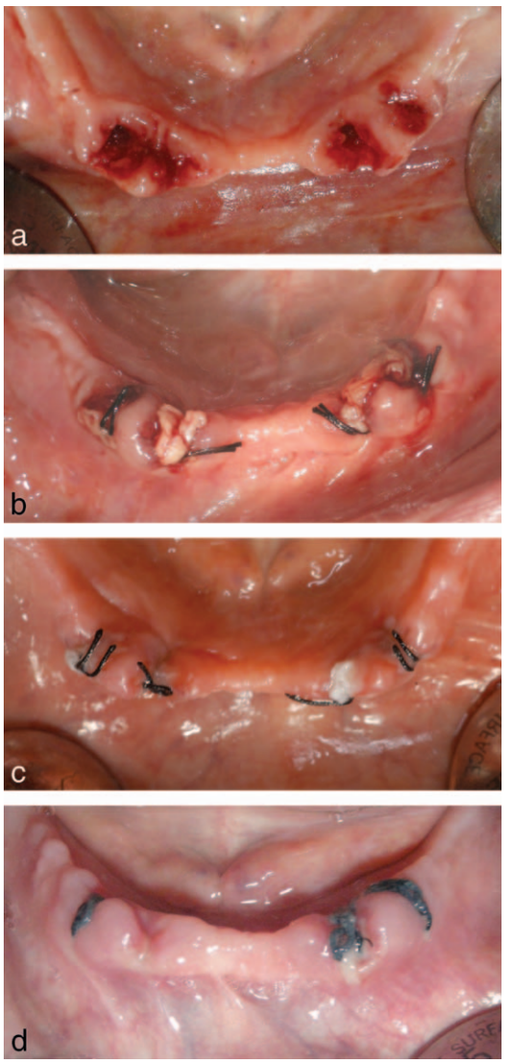

Figure 2. (A) Four postextraction sockets in the anterior mandible (33, 32, 42, 43) just after extraction in a patient who had undergone open heart surgery and was under anticoagulant therapy. (B) One PRF membrane was condensed in each extraction socket and maintained in position using a nonresorbable suture. (C) Soft tissue healing 24 hours after extraction and filling with PRF. The PRF membranes are still visible and look like a whitish plug on the extraction sockets. No delayed bleeding occurred. (D) At 72 hours after surgery, the extraction sockets are covered by a proliferative gingival tissue.

of tranexamic acid. In this study, we treated 14 patients with INR values >3.5, and no bleeding complications were reported in the remaining 12 patients.

Only 10 patients (20%) had mild postoperative bleeding (as defined by Souto et al[5]). In these patients the bleeding spontaneously resolved or was stopped using minimal compression with gauzes and hemostatic topical agents. This slight noncontinuous bleeding always stopped in the 2 hours after the surgical procedures. No case of delayed bleeding was reported.

The remaining 38 patients (76%) showed an adequate and complete hemostasis after dental extractions, that is, they experienced no hemorrhagic complications on the day of the extractions and in the following 2 days.

No cases of alveolitis were reported in the patients, and no patient complained about notable postsurgical pain. Moreover, a quick healing of the soft tissue around the postextraction defects was already noted 2 days after the surgery. All alveolar sockets were closed by a proliferating gingival tissue at the time of suture removal 1 week after surgery. After suture removal, no patients complained of residual pain or discomfort.

All of the patients were monitored at the medical and dental school (for dental care and/or hygiene) for at least 1 year after the dental extractions. No cases of endocarditis and no thromboembolic events or other postsurgical complications were observed in the experimental group.

Discussion

Compared to other studies, the 4% (n = 2) rate of hemorrhagic complications and 20% (n = 10) rate of mild bleeding may seem like a high prevalence of bleeding episodes. However, these results are also related to the thorough follow-up used in this study; patients were kept in the department for several hours after surgery. It is probable that the early 20% mild bleedings would have stopped alone, without our intervention, but we did not take any risks with these patients. Concerning the 4% hemorrhagic complications, the two patients (with INR of 3.7) in fact showed an immediate postoperative hemorrhage related to inadequate placement of PRF

TABLE 1
Study population

Year	Patient Age Range (Mean Years)	No. of Patients	Men/Women	No. of Extractions
2005	47 to 60 (52.5 ± 4.7)	15	7/8	53
2006	50 to 63 (54.5 ± 3.4)	20	11/9	76
2007	49 to 67 (56.5 ± 5.3)	15	4/11	39

gel, probably because alveolar residual bone was minimal and did not offer good retention for the PRF clot. These events were thus probably independent from the INR value. Still, in these patients, the hemorrhagic complications were resolved in a few hours using simple methods, that is, compression with sterile gauzes and local application of tranexamic acid.

The intramuscular antibiotic therapy was preferred to reduce the surgical complications (eg, pain, swelling, fever) after multiple dental extractions according to the hospital cardiologist's recommendations. But this was not the consensus procedure, and it was probably not the simplest choice. The desire to use a more classical antibiotic prophylaxis for this kind of patient was recently discussed with the cardiologists at the hospital. This situation illustrates the difficulty of changing habits when different departments are working together in big hospitals.

The clinical management of the heart surgery patients under anticoagulant therapy during dental extractions requires the practitioner to balance the risk of hemorrhagic complications against the risk of a more serious thromboembolic event.[37–39] Previous recommendations were to interrupt oral anticoagulant therapy before dental extractions to prevent hemorrhage. However, a review of the literature did not show well-documented cases of serious bleeding complications from oral surgery in patients receiving therapeutic levels of continuous warfarin sodium, whereas there were several cases of embolic complications in patients whose anticoagulant therapy was withdrawn before the dental extractions.[1,2] A recent survey showed that in more than 950 patients receiving continuous anticoagulant therapy and undergoing more than 2 400 oral surgical procedures, only 12 (1.3%) needed more than local treatments to control the hemorrhage.[40] The current consensus recommends avoiding the interruption of anticoagulant therapy and preventing hemorrhagic complications by the simple use of local measures, such as oxidized cellulose mesh and tranexamic acid,[9] fibrin

TABLE 2
Results of the study, sorted by international normalized ratio (INR) values

INR Value	Complications	Patient Age Range (Mean Years)	Men/Women	Nationality (Race)	No. of Extractions
2.0–2.5	2 mild postoperative bleeding	50 to 58 (53.4 ± 3.1)	4/5	Italian (white)	30
2.5–3.0	3 mild postoperative bleeding	49 to 65 (53.6 ± 4.2)	5/6	Italian (white)	39
3.0–3.5	5 mild postoperative bleeding	47 to 59 (54.3 ± 3.7)	7/9	Italian (white)	51
Over 3.5	2 hemorrhagic complications	49 to 67 (54.5 ± 4.5)	6/8	Italian (white)	48

adhesives, tranexamic acid on sterile gauze associated to mouth rinses for 1 week after the surgery, or even a PRP gel.[12,39,41–44]

The results of this study could validate the use of PRF during dental extractions for the prevention of postoperative bleeding in patients on anticoagulant therapy. However, numerous other techniques can lead to similar results; even if PRF is an inexpensive, easy, and quick procedure, it requires blood collection and handling. Oxidized cellulose mesh and tranexamic acid offer the same kind of antihemorrhagic results and are easy to handle. Still, the advantages of PRF are not only related to its antihemorrhagic properties; PRF is also a filling healing biomaterial[45,46] and accelerates wound closure. Its immune content may help protect the extraction sockets against unavoidable infections, and by enhancing soft tissue healing, PRF also reduces the duration of the contamination of the surgical site by oral bacteria. Finally, all other biomaterials become foreign bodies once contaminated, whereas a PRF clot always remains a natural filling material, that is, a natural optimized blood clot. There are no side effects and no significant discomfort and painful events.

The limitations of the present research are related to the small number of patients ($n = 50$) and the lack of a non-PRF control group. Ethical considerations did not allow us to evaluate the risk of bleeding without therapeutic intervention. However, from the archives of the department related to treatment of this kind of patients between 2005 and 2008, we know that the results with an absorbable oxidized cellulose mesh and tranexamic acid on gauze after sutures were very good in terms of hemorrhagic control: less than 5% of patients experienced mild postoperative bleeding, which was resolved using compression with gauzes and hemostatic topical agents. These results are very similar to the published data and the current consensus. However, postoperative pain or discomfort was often reported by the patients, and we also noticed some cases of alveolitis. Foreign materials inserted within fresh extraction sockets always disturb the healing process, whereas PRF, because it is a natural optimized blood clot, is completely tolerated.

Finally, despite the lack of a strictly comparable control group, the results of this study allowed us to validate PRF as filling and antihemorrhagic biomaterial during dental extractions in patients on anticoagulant therapy. The natural conclusion is also that compression with gauze with tranexamic acid may be the ideal complement to the use of PRF as filling biomaterial, particularly against early postoperative bleeding, even if it is often not necessary.

The production of PRF clots is easy and inexpensive; many potential applications are currently being developed and are slowly being introduced in different fields of human and animal medicine. These applications could be very useful, particularly in poor areas and developing countries. It is, for example, cheaper and easier to use PRF in patients on anticoagulant therapy than to use commercial fibrin glues. However, in the present application for dental extractions, many other inexpensive products can lead to similar results; the main advantage of PRF is that it is also an autologous healing biomaterial, a natural optimized blood clot.

PRF has plastic and soft tissue–adhesive properties, but this autologous material is first highly bioactive. A single PRF membrane slowly releases high amounts of growth factors (such as transforming growth factor, platelet-derived growth factor, vascular endothelial growth factor) and matrix proteins such as thrombospondin-1 (TSP-1) during at least 7 days.[22,47] Though TSP-1 is not properly a coagulation factor, it plays a significant role in the coagulation pathways. It functions as a matricellular protein, that is, it is not a structural matrix protein but it

modulates cell-matrix interactions. In conjunction with von Willebrand factor and fibrinogen, TSP-1 contributes to clot formation and even mediates an alternative/backup mechanism to von Willebrand factor.[48] Moreover, TSP-1 binds to von Willebrand factor and protects it from proteolysis,[49] thus maintaining the integrity of platelet aggregates. The slow release of this key molecule, and certainly many others, clearly contributes to the antihemorrhagic properties of the PRF clot. Thus, PRF could be tested in many other clinical situations in patients on anticoagulant therapy.

The slow release of molecules such as TSP-1 certainly explains the immediate antihemorrhagic properties of the PRF clot. However, in this study, no delayed bleeding was reported. Delayed bleeding is a significant problem with this kind of patients, and PRF allows this risk to be controlled. Indeed, the slow release of growth factors from the PRF membrane[22] and the strong fibrin architecture of the clot accelerate and improve soft tissue and bone healing.[19,23] As the wound closure is accelerated, delayed bleedings are logically avoided. Moreover, PRF is rich in leukocytes,[13,23] and these cells may be a significant asset for protecting the surgical sites against local infections and associated delayed healing.

It is important to note that quite normal PRF clots were produced in these patients under anticoagulant therapy. Thus, these medications do not seem to interfere significantly with the PRF natural polymerization in the blood collection tube. This result seems to confirm that the PRF production process is mechanically induced and not only biochemically driven, as even partially anticoagulated blood can be processed into PRF. From our experience, however, we must recommend increasing the centrifugation time in patients under anticoagulant therapy (18 minutes) to guarantee the collection of strong and reproducible PRF clots.

Finally, these results may open new treatment opportunities for implant placement after extraction in patients with general pathologies associated with delayed healing or coagulation. Indeed, the use of L-PRF for the protection of surgical sites in patients with these complex conditions combines antihemorrhagic effects with a significant healing stimulation of the tissues, and both effects are necessary for a successful treatment. This therapeutic approach has now to be tested and validated in various clinical situations.

Conclusions

The use of PRF as filling and antihemorrhagic biomaterial during dental extractions seems an efficient option in heart surgery patients under anticoagulant therapy. PRF is much cheaper than fibrin glues and most PRP kits available. This biomaterial, however, requires expert handling and is more complicated to prepare and use than oxidized cellulose gauze. The main advantage of PRF is its versatility: PRF has good antihemorrhagic properties and increases tissue healing and wound closure, thus allowing for a quick recovery without significant painful events. Many other applications of these antihemorrhagic and healing properties could be tested and evaluated in patients on anticoagulant therapy, particularly in oral implantology. Further research is required.

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