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Original Article

Evaluation of Platelet-Rich Fibrin and Platelet-Rich Plasma in Impacted Mandibular Third Molar Extraction Socket Healing and Bone Regeneration: A Split-Mouth Comparative Study

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Abstract

Objective: To compare the efficacy of platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) in postoperative extraction socket healing, pain, swelling, and bone regeneration after surgical removal of impacted mandibular third molars. **Materials and Methods:** The present split-mouth comparative study was conducted on 20 patients undergoing bilateral identical mandibular third molar extraction. PRF was placed on the right side of the third molar extraction socket, and PRP was placed on the contralateral side. Evaluation of soft tissue healing, pain, and swelling was carried out on immediate postoperative and on the 1st day, 3rd day, and 7th day. Radiological bone density was assessed on the 3rd and 6th months postoperatively. **Results:** Soft tissue healing was better in PRF site. The postoperative pain scores in PRF site were less compared with PRP site; however, there was no significant difference between immediate postoperative period ($P < 0.15$), 1st day ($P < 0.96$), 3rd day ($P < 0.58$), and 7th day ($P < 0.78$). Measurement of swelling on the 1st day ($P < 0.0020$) and 3rd day ($P < 0.0010$) showed significant difference on PRF site, but it ceases to nonsignificant on the 7th day ($P < 1.00$). Postoperative mean bone density at the 3rd and 6th months was higher in PRF site, which was statistically significant ($P < 0.00001$). **Conclusion:** Our results showed a significant improvement in the soft tissue wound healing and increase in bone density in PRF site than PRP site. There was significant reduction of the swelling found on the 1st and 3rd day at PRF site as compared to the PRP site. Although the postoperative pain scores were less in PRF site, this was not statistically significant among the two groups.

Keywords: Pain, platelet-rich fibrin, platelet-rich plasma, soft tissue healing, swelling, third molar

Introduction

Extraction of mandibular third molar is one of the most common surgical procedures performed in oral and maxillofacial surgery, which results in pain, swelling, and bony defect. Many attempts are being made to improve the postoperative recovery and patient quality of life after third molar surgery. Although several materials have been used to minimize the postoperative sequelae, autologous graft is still considered as the gold standard.[1] One such autologous bone graft material with abundance of growth factors that gained popularity in recent years is platelet concentrates such as platelet-rich plasma (PRP) and protein-rich fibrin (PRF).[2] The earlier studies found that the growth factors present in PRF and PRP enhance the healing and improve the postoperative recovery.[3,4]

PRP is an autologous concentrate of platelets suspended in plasma, which contains vital growth factors such as platelet-derived growth factors and transforming growth factor-beta 1 and 2 and vascular endothelial growth factors, all of which positively influence the repair and regeneration of tissues.[5,6] It is prepared by a two-stage centrifugation procedure

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by addition of anticoagulant or bovine thrombin that isolates the platelet concentrate. This is found to contain 6–8 times higher amount of growth factors as compared to normal blood. However, few researchers believe that the use of an anticoagulant to obtain PRP could be disadvantageous for wound healing.[7]

PRF is a next generation of platelet concentrate with autologous leukocytes, cytokines, structural glycoproteins, and a strong fibrin matrix which is prepared by simple method without adding any biochemical agent.[7] It contains leukocytes which provides adequate immunity and anti-infectious activities. In addition, the dense fibrous matrix polymerization mode of PRF creates a physiologic architecture favorable for wound healing.[8,9] Although many researchers have reported the role of PRF and PRP in wound healing of extraction sockets, we could not find any literature regarding the comparison of efficacy of PRF over PRP in split-mouth study in patients with bilateral mandibular third molar extraction cases. Hence, in this study, an attempt was made to assess the soft tissue healing, pain, swelling, and radiological bone density in patients undergoing identical bilateral third molar surgery using PRF and PRP.

Materials and Methods

A prospective split-mouth comparative study was conducted between June 2017 to May 2018 in the department of oral and maxillofacial surgery. The present study was a continuation of our previous research on PRP by incorporating the newer objective of comparing the effectiveness of PRF and PRP in healing of extraction socket and bone regeneration.[5]

A total of 20 patients who had identical bilateral mandibular impaction type and similar difficulty level and who agreed to come for follow-up visits were included. Written informed consent was obtained for complete diagnostic workup and extraction of third molars. The difficulty of mandibular third molar extraction was evaluated using the index given by Pederson,[10] and the extraction with the same difficulty level was included in both the groups.

Digital panoramic radiographs were taken pre- and postoperatively. PRF was placed on the right side of the third molar extraction socket, and PRP was placed on the left side. Postoperative evaluation of soft tissue healing, pain, swelling, and radiological bone density was carried out. Healthy patients (American Society of Anesthesiologists I and II) and patients with similar difficulty level of impacted mandibular third molars were included in the study.

Exclusion criteria

- Patients with localized infection in the region of lower third molars
- Patients with immune compromised status or systemic disease which might affect normal healing process
- Patients with adverse oral habits such as smoking and alcohol
- Patients with platelet count <150,000/cu.mm and history of bleeding disorder
- Patient taking any medication that influences the healing.

Preparation of PRF was carried out according to the technique described by Dohan *et al*. in clinical setting and immediately placed in the socket area.[11]

Under aseptic techniques, 6 ml of blood was drawn intravenously from the antecubital region of patients using flashback blood collection needle and BD Vacutainer without anticoagulant. The collected blood was centrifuged at 3000 rpm for 10 min. The resultant product consisted of following three layers:

- Top most layer consisted of acellular platelet-poor plasma (PPP)
- PRF clot in the middle
- Red blood cells (RBCs) at the bottom.

The topmost layer of PPP was discarded. PRF and the uppermost layer of RBCs were isolated and used in extraction socket.

Preparation of platelet-rich plasma

PRP is prepared by a process known as differential centrifugation. In differential centrifugation, acceleration force is adjusted to sediment certain cellular constituents based on different specific gravity.[12]

Six milliliters of intravenous blood was collected in BD Vacutainer containing citrate phosphate dextrose adenine solution and centrifuged at 1200 rpm for 10 min. The result was separation of the whole blood into a lower RBC region and upper straw-colored plasma. This plasma contains relatively low concentration of platelets in the uppermost region and higher concentration of platelets in the boundary layer often called as "buffy coat." PPP, buffy coat, and upper 1 ml RBC layer was collected in a borosilicate glass tube and centrifuged at 2000 rpm for 10 min. The upper half of the supernatant was discarded, and the lower half was mixed to yield PRP and transferred into a clean sterile stainless-steel bowl, and 0.5–1 ml of 10% calcium chloride was added to the PRP, leading to formation of PRP gel.

Surgical technique for the removal of bilateral impacted mandibular third molar

Under aseptic precautions, 2% lignocaine hydrochloride with 1:200,000 adrenaline was administered using the conventional inferior alveolar nerve block to anesthetize the mandibular third molar area. A mucoperiosteal flap was raised after the standard classical ward incision. Bone on the buccal and the distal aspect of the impacted tooth was removed using a round bur. Odontectomy was done whenever required to facilitate extraction. The impacted tooth was removed using the elevators, and sharp bony edges were removed. The extraction socket was irrigated with 0.5% diluted povidone iodine and saline. Complete hemostasis was achieved, and primary wound closure was done using 3-0 black silk by interrupted sutures [Figure 1]. Standard postextraction instructions along with the antibiotics (capsule amoxicillin 500 mg TDS for 5 days) and analgesics (tablet diclofenac 50 mg BD for 3 days) were prescribed. The operator and examiners were blinded. All the

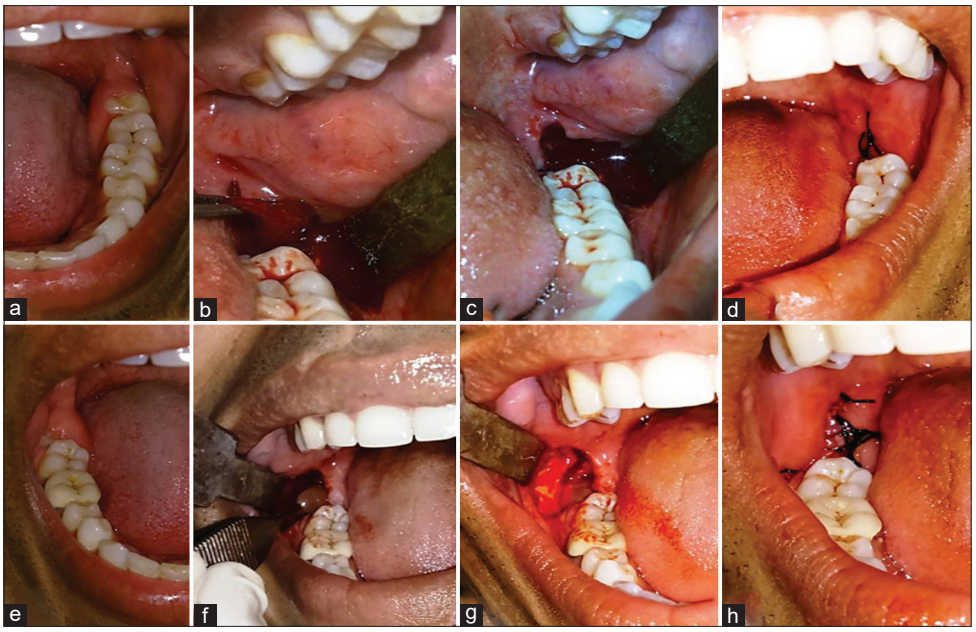

Figure 1: Photograph showing steps of surgical removal of left and right impacted third molars and placement of platelet-rich plasma and PRF. (a) Left impacted third molar socket, (b) platelet-rich plasma being placed in the third molar socket, (c) platelet-rich plasma in the socket, (d) wound closed with 3-black silk interrupted sutures. (e) Right impacted third molar, (f) PRF being placed in the third molar socket, (g) PRF in the socket, (h) wound closed with 3-black silk interrupted sutures

extractions were carried out by single experienced oral surgeon using the same sets of sterilized equipment in all extractions. Postoperative measurement of soft tissue healing, pain, and swelling was performed by another experienced oral surgeon.

Postoperative measurement of soft tissue healing, pain, and swelling

The soft tissue healing, pain, and swelling were measured on immediate postoperative and on the 1st, 3rd, and 7th postoperative days. Soft tissue healing was assessed as per the healing index given by Landry *et al*.[13] The parameters evaluated include the change of tissue color more than 50% gingival red, bleeding on palpation, and granulation tissue formation.

Pain intensity was assessed using a 10-level visual analog scale (VAS) with the patient placing a mark on the scale to indicate an intensity range from no pain (0) to severe/unbearable pain (10).

Pre- and post-operative swelling was assessed using a flexible plastic millimeter measuring tape. The permanent markings were made prior to surgery on the following facial landmarks, lower attachment of the ear lobe, ala of the nose, outer canthus of the eye, and angle of the mandible. The horizontal dimension of swelling was measured from the lower attachment of the ear lobe to the ala of the nose, and the vertical dimension of swelling was measured from the outer cantus of the eye to the angle of the mandible using the measuring tape [Figure 2].

The facial measurement was made preoperatively and on the 1st, 3rd, and 7th days postoperatively. The measurement of swelling was determined by subtracting postoperative facial measurement from preoperative facial measurement

Figure 2: Photograph showing horizontal and vertical measurement of face

and calculating the percentage swelling to rule out individual differences in facial dimension.

Bone density was assessed using digital panoramic radiograph (Orthopantomography) on the 3rd and 6th months postoperatively. The mean gray-level histogram values of the OPG of the extraction socket were obtained through adobe Photoshop 7.0 software, Adobe Inc. San Jose, California, U.S.

Procedure: The scanned OPG image was imported to adobe Photoshop 7.0, and histogram tool in software was selected to draw the outline of the socket. The cursor was placed at the center of the socket and the mean value of the selected area was recorded. The difference in the mean gray-level values at PRF and PRP sites was tabulated and compared [Figure 3].

Results

The present study consisted of total 20 patients, of which 7 (35%) were male and 13 (65%) were female patients, with a mean age of 22 years [Table 1].

Assessment of soft tissue healing

At the PRF site, there were no patients with tissue color more than 50% gingival red, bleeding on palpation, or granulation tissue formation on the 1st, 3rd, and 7th postoperative days. At the PRP site, tissue color more than 50% red was present in two patients on the 1st day, bleeding on palpation was present in two patients on the 1st day, and granulation tissue was present in one patient on the 7th day. Soft tissue healing was significantly better in PRF site compared to PRP site [Table 2].

Assessment of pain by visual analog scale

Immediate postoperative evaluation showed mean pain score of 1.9 in PRF site and 2.3 in PRP site, 1.8 in PRF site and 2.3 in PRP site on the 1st day, 2.2 in PRF site and 2.7 in PRP site on the 3rd day, and on the 7th day the score was 0 in PRF site and 0.1 in PRP site. Postoperative pain scores were less in PRF site as compared to PRP site; however, Mann–Whitney U-test showed no significant difference between both the groups on immediate postoperative period ($P < 0.15$) and on the 1st day ($P < 0.96$), 3rd day ($P < 0.58$), and 7th day ($P < 0.78$) [Table 3].

Assessment of swelling

On the 1st day, the mean dimension of swelling was 9.83 cm in PRF site and 9.92 cm in PRP site. On the 3rd day, it was 9.92 in PRF site 10.06 in PRP site. On the 7th day, it was 9.68 in PRF site and 9.68 in PRP site. Significant reduction of the swelling was found in PRF site on the 1st day ($P < 0.0020$) and 3rd day ($P < 0.0010$); however, the facial measurements recorded on the 7th day showed no statistically significant differences between the two groups ($P < 1.00$) [Table 4].

Radiological assessment

The mean bone density score on the 3rd month in PRF site was 135.16 and in PRP site was 132.49 and on the 6th month in PRF site was 140.57 and PRP site was 135.92. Significant improvement in bone density in PRF site was noticed on the 3rd month ($P < 0.00001$) and 6th month ($P < 0.00001$) postoperatively [Table 5].

Table 1: Gender and mean age distribution of patient

Gender	Number of patients (%)	Mean age	SD
Male	7 (35)	26.43	7.44
Female	13 (65)	25.77	6.89
Total	20 (100)	26.00	6.90

SD: Standard deviation

Discussion

Healing is a complex biological process which involves participation of many cells and growth factors. The platelets are activated by coagulation cascade, particularly thrombin and subendothelial collagen. These platelets contain several growth factors, which stimulates biological functions such as chemotaxis, angiogenesis, proliferation, differentiation, and modulation, which affects the wound healing and regeneration. The application of autologous PRP in oral and maxillofacial surgery was popularized by Marx.[14]

PRP and PRF are the autologous concentrates of platelets predominately used in oral and maxillofacial surgery and periodontology to enhance the healing process and to minimize the potential postoperative complications.[14-16] Earlier research suggested that the platelet-rich concentrates have optimistic effects to jump start the cascade of osteogenesis by providing vital growth factors, bone morphogenetic proteins, and early consolidation of the graft, all of which accelerate the mineralization of the graft.[17] In addition, platelet concentrates may be used alone or in combination with bone grafts such as calcium sulfate hemihydrate as a socket preservation material and for the treatment of periodontal bony defects.

Soft tissue healing was assessed as per the healing index given by Landry *et al*.,[13] on the 1st, 3rd, and 7th postoperative days after placement of PRF and PRP. The soft tissue healing was superior at PRF site than PRP site on all postoperative days. These results were supported by Yelamali and Saikrishna[18] who noticed a significant difference in the PRF site as compared to PRP site. Doiphode *et al*.[19] found no evidence of wounds dehiscence in PRF site as compared to control and PRP site. This signifies

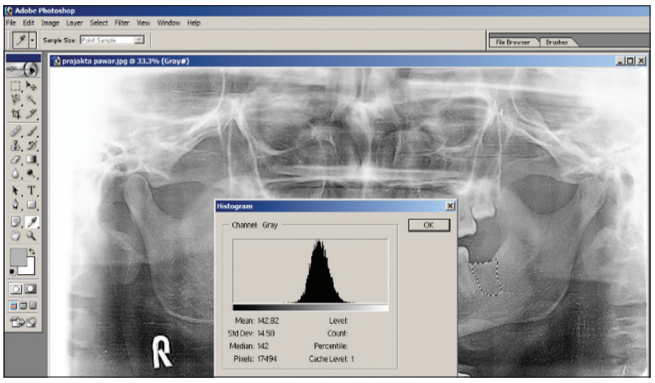

Figure 3: OPG showing gray-level histogram on a left third molar extraction socket

Table 2: Comparison of PRF and PRP site with tissue color more than 50% gingival red, bleeding on palpation, and granulation tissue

Groups	Tissue color >50% gingival red			Bleeding on palpation			Granulation tissue		
	1st day	3rd day	7th day	1st day	3rd day	7th day	1st day	3rd day	7th day
PRF site	0	0	0	0	0	0	0	0	0
PRP site	2	0	0	2	0	0	0	0	1

PRP: Platelet-rich plasma, PRF: Platelet-rich fibrin

Table 3: Comparison of PRF and PRP site with respect to visual analog scale scores at immediate postoperative after local anesthesia worn off, 1st day, 3rd day, and 7th day by Mann-Whitney U-test

Groups	Immediate postoperative		1st day		3rd day		7th day		Changes from immediate postoperative to					
									1st day		3rd day		7th day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PRF	1.9	0.9	1.8	0.7	2.2	0.7	0.0	0.0	0.1	0.9	−0.3	1.1	1.9	0.9
PRP	2.3	0.7	2.3	0.8	2.7	1.0	0.1	0.2	0.0	1.0	−0.5	1.2	2.2	0.8
Percentage of change in PRF site									5.3%#	*P*=0.6241	13.2%#	*P*=0.3259	100.0%#	*P*=0.0001*
Percentage of change in PRP site									03.0%#	*P*=0.9687	20.0%#	*P*=0.1235	97.8%#	*P*=0.0001*
Z	−1.4066		−1.6636		−1.8935		−0.2705		−0.0541		−0.4463		−1.1902	
P	0.1596		0.0962		0.0583		0.7868		0.9569		0.6554		0.2340	

*$P<0.05$, #Applied Wilcoxon matched pairs test. PRP: Platelet-rich plasma, SD: Standard deviation

Table 4: Comparison of PRF and PRP site with respect to vertical swelling (cm) scores at immediate preoperative, 1st day, 3rd day, and 7th day by paired *t*-test

Groups	Immediate preoperative		1st day		3rd day		7th day		Changes from immediate preoperative to					
									1st day		3rd day		7th day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PRF	9.68	0.93	9.83	0.95	9.92	0.95	9.68	0.93	0.15	0.08	0.24	0.11	0.00	0.00
PRP	9.68	0.93	9.92	0.98	10.06	0.96	9.68	0.93	0.24	0.09	0.38	0.14	0.00	0.00
Percentage of change in PRF site									1.5%#	*P*=0.0001*	2.5%#	*P*=0.0001*	0.0%#	-
Percentage of change in PRP site									2.5%#	*P*=0.0001*	3.9%#	*P*=0.0001*	0.0%#	-
t	0.0000		−0.2941		−0.4634		0.0000		−3.3275		−3.5835		-	
P	1.0000		0.7703		0.6457		1.0000		0.0020*		0.0010*		-	

*$P<0.05$, #Applied paired *t*-test. PRP: Platelet-rich plasma, SD: Standard deviation

Table 5: Comparison of PRF and PRP site with respect to bone density scores at 3rd and 6 months by paired *t*-test

Groups	3 months		6 months		Changes from 3rd day to			
					3 months		6 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PRF	135.16	4.41	140.57	4.52	8.09	2.56	13.50	2.58
PRP	132.49	4.36	135.92	4.34	4.46	1.26	7.89	1.39
Percentage of change in PRF site					6.4%#	*P*=0.0001*	10.6%#	*P*=0.0001*
Percentage of change in PRP site					3.5%#	*P*=0.0001*	6.2%#	*P*=0.0001*
t	1.9269		3.3147		5.6937		8.5485	
P	0.0615		0.0020*		0.00001*		0.00001*	

*$P<0.05$, #Applied paired *t*-test. PRP: Platelet-rich plasma, SD: Standard deviation

a better soft tissue healing of extraction sockets with PRF as compared to the PRP. In contrast, Dutta *et al*.[20] reported slightly better soft tissue healing in PRP site compared to PRF site on the 3rd day, 7th day, and 14th day postoperatively; however, there was no statistical significant difference between the two groups.

This is due the fact that PRF clot forms a strong fibrin matrix with a comple × 3-dimensional architecture which dissolves slowly similar to the natural blood clot and it also releases growth factors in more controlled manner over long term. Furthermore, it is an autologous soluble biologic material which is prepared without the addition of any foreign bodies; hence, it prevents the consequent foreign-body inflammatory responses.[21,22] The postoperative pain was assessed using VAS on immediate postoperatively and on the 1st, 3rd, and 7th postoperative days. Although the pain scores were relatively lesser on postoperative days in PRF site, these scores were not statistically significant. This was in accordance with the study by Unakalkar *et al*.,[23] who also reported no significant differences between PRF and PRP sites. However, contrast

findings were reported by Daugela *et al*.,[24] and Dutta *et al*.[20] noticed a significant reduction of pain on the 1st postoperative week in PRF site as compared to PRP site. The accurate assessment of pain in split-mouth design would be difficult as there is overlapping of pain due to the carry-across effect from one site to another site in this study design.

Assessment of swelling was carried out on the 1st day, 3rd day, and 7th day postoperatively. The mean dimension of swelling was significantly lesser on the 1st day and 3rd day on PRF site, which was statistically significant. However, on the 7th day, no significant changes were observed in both the sites. PRF may provide significant reduction of swelling in shorter time compared to PRP. These findings were supported by Daugela *et al*.,[24] who noticed significant reduction of facial swelling on the 1st and 3rd postoperative days in PRF which ceases to nonsignificant at day 7. Dutta *et al*.[20] reported a significant reduction of swelling on PRF site on the 3rd, 7th, and 14th day postoperatively. In contrast, a study by Unakalkar *et al*.[23] observed slightly better reduction of swelling in PRP group than PRF group on the 7th postoperative day. However, these findings were nonsignificant in both the groups.

The mean bone density scores were recorded at the 3rd month and 6th month using digital panoramic radiographs. Statistically significant difference was found in PRF site on the 3rd and 6th months. This finding was in accordance with the study by Yelamali and Saikrishna;[18] they noticed that the mean values of bone density in PRF group were significantly higher than PRP group. Similar findings were observed by Dutta *et al*.;[20] bone healing index was significantly higher in PRF site on the 1st month, 3rd month, and 6th month. The autologous growth factors present in PRF have stronger and more durable effect on proliferation and differentiation of osteoblasts.[25]

This signifies the use of PRF over other platelet concentrates as it releases the growth factors at a sustained rate over a longer period, thereby optimizing wound healing.[26,27] The main advantage of PRF is that it is prepared naturally without addition of thrombin, and it is hypothesized that PRF has a natural fibrin framework and can protect growth factors from proteolysis. Thus, growth factors can keep their activity for a relatively longer period and stimulate bone regeneration effectively.[28] The limitations of the present split-mouth study include small sample size and absence of control group as it was difficult to recruit the cases with bilateral impacted teeth with similar difficulty level. In addition, the inclusion and exclusion criteria of our study further resulted in difficulty in enrolling the cases. The present study was done with a follow-up of 6 months which was adequate to evaluate the effects of PRF and PRP. However, further histological studies to evaluate the bone and randomized trials are required to check the efficacy of these platelet concentrates to get conclusive results.

Conclusion

Our results showed a significant improvement in the soft tissue wound healing and increase in bone density in PRF site. Although the postoperative pain scores were less and reduction of swelling was noticed in initial days in PRF site, this was not significant between two groups. This clearly signifies that the PRF has better hard and soft tissue healing properties than PRP.

Ethical approval

The ethical clearance was obtained from the institutional ethical committee and written informed consent was taken from the patient for complete diagnostic workup and extraction of mandibular third molar. Patient consent was also obtained for publication of their data.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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