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· 临床研究 ·

富血小板纤维蛋白对正畸牙移动影响的系统评价

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【摘要】 目的 评估富血小板纤维蛋白(platelet-rich fibrin, PRF)对正畸牙移动的影响,为临床应用提供依据。**方法** 通过检索7个电子数据库,以及手动检索方法,检索报道在正畸牙移动中使用PRF的随机对照临床试验。使用Cochrane偏倚风险评估工具对纳入研究进行偏倚风险评估。最终,由于各研究中患者临床特征和研究方法的异质性,所以采用定性的方法对结果进行总结和描述。**结果** 共纳入6篇研究;其中5篇为自身对照设计试验,1篇为平行对照试验;2篇使用富白细胞PRF,4篇使用可注射PRF;3项研究的偏倚风险评估为“有一定风险”,3项研究为“低风险”;试验周期最短为4周,最长为5个月;4项研究结论支持PRF可加速正畸牙移动,1篇文献表明PRF无影响,1篇文献显示PRF抑制正畸牙移动;中等质量的证据表明PRF在使用前3个月可加速正畸牙移动,而低质量的证据支持PRF在使用4个月后将失去其促进正畸牙移动的作用。**结论** 目前的证据显示,PRF早期可促进正畸牙移动,然而其长效作用仍有待进一步探究。

【关键词】 错殆畸形; 正畸; 拔牙矫治; 牙移动; 富血小板纤维蛋白; 浓缩血小板; 生长因子; 局部应用; 随机对照试验; 系统评价

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Effect of platelet-rich fibrin on orthodontic tooth movement: a systematic review YAO Ke, WU Yongzhi, ZHAO Zhihe. State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

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【Abstract】 Objective To evaluate the effect of platelet-rich fibrin (PRF) on orthodontic tooth movement (OTM) and to provide a basis for clinical application. **Methods** Literature searches were conducted in 7 electronic databases supplemented with a hand search. Randomized controlled trials focusing on OTM with PRF were included. The risk of bias was assessed by the Cochrane tool. Finally, due to the heterogeneity of patient clinical characteristics and research methods, the results in every study were qualitatively described. **Results** Six studies were included. Five studies were split-mouth designs, and 1 was a two-arm parallel design. Two studies used leukocyte- and platelet-rich fibrin, while the other 4 used injectable PRF. The risk of bias of 3 studies was graded as “Some concerns”, and 3 were graded as “Low risk”. The trials lasted from 4 weeks to 5 months. Four studies supported that PRF could accelerate OTM, 1 study demonstrated that PRF had no effect on OTM, and 1 study reported that PRF decreased OTM. There is moderate-quality evidence that PRF accelerates OTM in the first 3 months after application, while low-quality evidence supports that PRF loses its tooth-acceleration effect after 4 months. **Conclusion** Limited clinical evidence suggests that PRF could accelerate OTM in the early stages, but its long-term effect needs clarification.

【Key words】 malocclusion; orthodontics; tooth extraction; tooth movement; platelet-rich fibrin; platelet concentrate; growth factor; local application; randomized controlled trials; systematic review

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错𪚩畸形一般指在生长发育过程中由遗传和环境因素导致的牙齿、颌骨和颅面畸形。据报道,错𪚩畸形的患病率高达54%^[1]。正畸治疗不仅有利于恢复患者的口颌面功能,也有利于改善患者的容貌,提高患者的生活质量^[2]。但漫长的治疗周期往往成为患者最为关注的问题之一。综合的正畸治疗一般持续2~3年,这不仅会降低患者的依从性,也会造成如龋齿、牙根吸收、牙周病等一系列并发症^[3-4]。因此,加速牙齿移动和缩短治疗周期成为了患者和医生的共同目标。

牙齿移动的速度很大程度上取决于牙槽骨-牙周膜复合体的改建速度^[5-6]。加速牙移动的原理包括促进炎症因子的表达、加快骨重塑和增强牙槽骨改建代谢过程等^[7-8]。近年来,一系列手段包括手术和非手术方法被提出,以期加快正畸牙齿移动,缩短正畸疗程^[5,9]。在这些方法中,富血小板纤维蛋白(platelet-rich fibrin, PRF)具有微创、无系统性副作用等优点备受关注。PRF是第二代富血小板浓度物,相比于富血小板血浆,具有更易制备和作用时间更长的特点^[10]。其持续释放的各种生长因子、细胞因子等物质,有利于细胞增殖、分化、迁移、黏附等众多生物过程,并最终促进组织改建^[11]。由于PRF制备的简便性和优越的生物特性,PRF具有极高的临床应用价值。但目前PRF对加速正畸牙移动的临床效果尚不清楚。因此,本研究通过回顾当前关于PRF与正畸牙移动关系的随机对照临床试验,系统全面地评估PRF加速正畸牙移动的有效性,为其临床应用提供依据。

1 资料和方法

1.1 纳入与排除标准

1.1.1 纳入标准 ①研究设计:随机对照临床试验(randomized controlled trial, RCT);②研究对象:初次接受正畸拔牙固定矫治的错𪚩畸形患者;③干预方式:PRF局部注射或放置于正畸患者牙周组织内;④对照方式:空白对照,单纯常规正畸治疗,未使用其他影响正畸牙移动的辅助措施;⑤结果指标:正畸牙齿移动距离或速率。

1.1.2 排除标准 ①患者二次正畸治疗;②同一患

者同时使用PRF及其他辅助正畸牙移动措施;③患者口腔卫生不佳,患有牙周疾病、系统性疾病或唇腭裂等颅颌面综合征;④非随机对照试验、队列研究、病例对照研究、病例报告及综述类文献。

1.2 检索策略

计算机检索PubMed、Cochrane Library、Embase、Web of Science、欧洲灰色文献信息系统、中国知网、中国生物医学文献数据库等7个电子数据库,另外对可能纳入的文献及相关的综述文献的参考文献进行手动检索。检索截止时间为2022年1月。检索方式采用主题词结合自由词的方式检索,检索过程无语言限制。检索词包括:正畸(orthodontics)、牙移动(tooth movement)、富血小板纤维蛋白(platelet-rich fibrin)。

1.3 文献筛选与数据提取

根据纳入标准,2名研究员独立筛选文献、提取数据并交叉核对,如有分歧则通过与第3名研究者讨论解决。首先,去除重复文献后,2名研究者通过阅读文献标题和摘要初步筛选可能纳入的文献,而后通过阅读这些文献的全文,确定纳入的文献。提取的数据包括:作者、发表时间、国籍、研究设计、患者情况、治疗措施及研究的主要结果。

1.4 偏倚风险评价

2名研究者分别独立使用Cochrane偏倚风险评估工具第二版(RoB 2)^[12]对所纳入文献进行偏倚风险评估。主要针对以下5个方面进行评价:随机化过程中的偏倚、偏离既定干预措施的偏倚、结局数据缺失的偏倚、结局测量的偏倚和选择性报告结果的偏倚。其中,每个方面的偏倚风险可分为3个等级:低风险、有一定风险和高风险。对于任一个研究,若所有领域的偏倚风险评估均为“低风险”,则该研究的总体偏倚风险为“低风险”;若有任意领域为“有一定风险”且不存在“高风险”的领域,则总体偏倚风险为“有一定风险”;若有任意一个领域被评估为“高风险”,则该研究总体偏倚风险为“高风险”。

1.5 数据分析

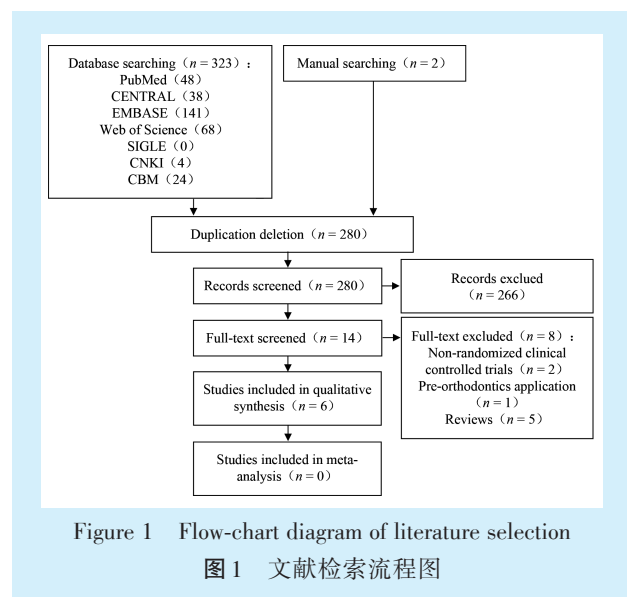
通过Q检验对纳入研究进行异质性检验,用I²指数评价异质性大小。若I²>50%,认为异质性较

高,采用随机效应模型进行Meta分析;反之,使用固定效应模型^[13]。若纳入研究异质性过大而不宜合并数据,则采用描述性语言阐释结果。最终,根据证据推荐分级的推荐、制定与评估(Grading of Recommendation, Assessment, Development and Evaluation, GRADE)标准对结局证据进行评级^[14]。

2 结果

2.1 文献检索结果

通过电子检索数据库,加上手动检索的文献,共获得325篇相关文献,去除重复后剩余280篇文献。通过阅读文章标题及摘要,共排除266篇文献。对剩余14篇文献进行全文阅读后,共纳入6篇文献^[15-20]。检索过程如图1所示。



2.2 纳入研究的基本特征

纳入的6项研究中,有5篇均采用自身对照设计^[15, 16, 18-20],剩余1篇采用的是平行对照设计^[17];试验持续的时间最短为4周^[17],最长为5个月^[15, 19];2项研究分别在拔牙窝内放置富白细胞和血小板的纤维蛋白(leukocyte- and platelet-rich fibrin, L-PRF)块^[20]和膜^[19],另外4项研究采用黏膜下注射^[15-16]或牙周膜内注射^[17-18]PRF液(injectable platelet-rich fibrin, i-PRF)的方式。在评价牙移动的方式上,1项研究采用测量间隙关闭量^[20],1项研究采用测量侧切牙内收量^[17],3项研究采用了尖牙远移量^[15, 18, 19],1项研究同时测量间隙关闭和尖牙远移的数据^[16]。纳入研究的基本信息见表1。

2.3 偏倚风险评估

使用RoB 2工具评估所纳入的6篇RCT的偏

倚风险(表2)。3篇文献分别在“偏离既定干预措施”^[20]、“结果测量”^[18-19]、“选择性报告结果”^[19-20]方面“有一定风险”,而最终总偏倚风险评估为“有一定风险”。另外3项研究则被评为“低风险”^[15-17]。

2.4 结果描述

由于纳入研究在患者临床特征、PRF制备及应用方法以及牙移动测量方法和时间上的差异等,不适宜进行数据合并,因此本研究拟对研究结果进行描述性分析。

对于PRF是否加速正畸牙移动的问题,纳入的6项研究结论有所差异。其中,4项研究认为PRF可加速正畸牙移动:Karci等^[16]发现,在注射PRF12周后,试验组尖牙远移量和间隙关闭量均比对照组大;Karakasli等^[17]在切牙内收前和内收后第2周注射PRF,4周内试验组切牙内收量均大于对照组,并且在注射PRF后第1周内牙齿移动量大于第2周;同样是在尖牙远移的第0周和第2周注射PRF, Erdur等^[18]研究发现在尖牙远移开始后12周内,注射PRF侧的尖牙远移量均大于对照侧;Tehranchi等^[20]在拔牙窝内放置L-PRF,发现L-PRF有助于加速正畸牙移动。另外2项研究则给出了不同的结果:Zeitounlouian等^[15]发现注射PRF后,正畸牙移动速率仅在第2个月快于对照组,并且两者在5个月的牙齿移动总量上没有差别(表3,表4);在另一项同样历时5个月的研究中,Pacheco等^[19]却发现L-PRF膜处理组的平均牙齿移动速率小于对照组。

PRF对正畸牙移动影响证据的质量评价显示,中等质量的证据表明,PRF在前3个月能促进正畸牙移动,而低质量的证据支持PRF在使用后4个月以上将失去作用。

3 讨论

PRF复杂的纤维蛋白网状结构,使其具有更多的生长因子等物质,并且具有更长作用时间的优点^[21]。因此,PRF被用于促进组织再生和修复^[22-23]。近年来,众多学者也在探索PRF在正畸领域的应用前景,例如减少牙根吸收^[24]、提高术后稳定性^[25]、颞下颌关节紊乱病^[26]等。

本次纳入的关于PRF对正畸牙齿移动影响的研究中,各研究得到的结论不尽相同。4项研究支持PRF能够加速正畸牙移动的效果^[16-18, 20],1项研究称PRF对正畸牙移动没有显著影响^[15],而另1项研究则发现正畸中使用PRF会降低牙齿移动速

表1 纳入研究主要特征
Table 1 Characteristics of included studies

Study	Country	Study design	Sample size	Gender (male/female)	Age/year	Malocclusion	Group (PRF/control)	Trial duration	Orthodontic force/g
Tehranchi 2018 ^[20]	Iran	split-mouth	8	5:3	17.37(12-25)	NR	8:8	16 weeks	NR
Pacheco 2020 ^[19]	Brazil	split-mouth	17	5:12	33(20-45)	Angle Class I (14) Angle Class II Division 1(3)	17:17	5 months	150
Karci 2021 ^[16]	Turkey	split-mouth	12	5:7	16.45 ± 0.27	Angle Class II	12:12	12 weeks	150
Erdur 2021 ^[18]	Turkey	split-mouth	20	8:12	21.4 ± 2.9	Angle Class II Division 1	20:20	12 weeks	150
Karakasli 2021 ^[17]	Turkey	two-arm parallel	40	17:23	20.7 ± 1.45	Angle Class II Division 1	20:20	4 weeks	150
Zeitounlouian 2021 ^[15]	Syria	split-mouth	21	6:15	20.85 ± 3.85	Angle Class II Division 1	21:21	5 months	150

Study	PRF type	PRF preparation method	PRF application method	PRF time	PRF dosage /mL	Measurement method	Measurement time	Results
Tehranchi 2018 ^[20]	L-PRF plot	2 700 r/min, 12 min	Tooth extraction socket; filling and sutured	0 day	NR	Space closure; plaster cast	0, 2, 4, 6, 8, 10, 12, 14, 16 weeks	L-PRF > control
Pacheco 2020 ^[19]	L-PRF membrane	2 700 r/min, 14 min	Tooth extraction socket; filling and sutured	-15 days	NR	Canine distalization; intraoral	0, 5 months	L-PRF < control
Karci 2021 ^[16]	Injectable PRF	800 r/min, 3 min	Canine buccal, palatal, distal attached gingiva; submucosal injection	0, 4, 8 weeks	0.7	Space closure, canine distalization; digital oral scan modal	0, 2, 4, 6, 8, 10, 12 weeks	i-PRF > control
Erdur 2021 ^[18]	Injectable PRF	700 r/min, 3 min	Canine distobuccal and distopalatal sites; intraligamental injection	0, 2 weeks	4	Canine distalization; plaster cast	0, 1, 4, 8, 12 weeks	i-PRF > control
Karakasli 2021 ^[17]	Injectable PRF	700 r/min, 3 min	Incisor; intraligamental injection	0, 2 weeks	2-3	Lateral incisor retraction; plaster cast	0, 1, 2, 3, 4 weeks	i-PRF > control
Zeitounlouian 2021 ^[15]	Injectable PRF	700 r/min, 3 min	Tooth extraction socket buccal and palatal attached gingiva; submucosal injection	0, 1 months	3	Canine distalization; plaster cast	0, 1, 2, 3, 4, 5 months	i-PRF=control

PRF: platelet-rich fibrin; i-PRF: injectable platelet-rich fibrin; L-PRF: leukocyte- and platelet-rich fibrin; NR: not reported

表2 纳入研究偏倚风险
Table 2 Risk of bias assessment of included studies

Study	Randomization process	Intended interventions	Missing outcome data	Outcome measurement	Selected reported result	Overall assessment
Tehranchi 2018 ^[20]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Pacheco 2020 ^[19]	Low	Low	Low	Some concerns	Some concerns	Some concerns
Karci 2020 ^[16]	Low	Low	Low	Low	Low	Low
Erdur 2021 ^[18]	Low	Low	Low	Some concerns	Low	Some concerns
Karakasli 2021 ^[17]	Low	Low	Low	Low	Low	Low
Zeitounlouian 2021 ^[15]	Low	Low	Low	Low	Low	Low

率^[19]。这些研究结论的差异可能与患者的数量 and 特征、结局测量的时间和方法有关,另外,也与 PRF 的制备方法、应用时间和剂量有关^[27]。

当笔者将研究根据不同时间段分析时,得到了较有意义的结果。在使用 PRF 的前3个月,PRF 能加速正畸牙移动,并且在第2个月最为明显^[15, 16, 18, 20];在使用 PRF 4个月以上后,2项研究均报道试验组和对照组在结束时牙齿移动总量相

似^[15, 20],而另1项研究则表明使用 PRF 5个月后牙齿移动总量小于对照组^[19]。这些研究结果表明,在正畸中使用 PRF 早期,牙移动速度加快,然而经过一段时间后,使用 PRF 组和对照组的牙移动速度则没有了差别,甚至使用 PRF 组的牙齿移动速度较慢。但是,在另一项长达6个月的前瞻性队列研究中,研究者表明在拔牙窝内放置 PRF 6个月后仍然能够促进牙齿移动^[28]。笔者更倾向于正畸单

表3 PRF对正畸牙移动量的影响

Table 3 Effect of PRF on orthodontic tooth movement

 $\bar{x} \pm s$

Overall time	Study	<i>n</i>	PRF group	Control group	Mean difference (95% CI)	<i>P</i>
0-1 week	Erdur ^[18]	20	0.73 ± 0.11	0.35 ± 0.08	-	0.001
	Karakasli ^[17]	40	0.14 ± 0.03	0.08 ± 0.02	-	0.001
0-1 month	Karakasli ^[17]	40	0.50 ± 0.11	0.30 ± 0.06	-	0.001
	Zeitounlouian ^[15]	21	0.92 ± 0.56	1.25 ± 0.99	-0.33 (-0.80, 0.13)	0.157
0-3 months	Karci ^[16]	12	2.83 ± 0.21	2.04 ± 0.22	-	0.011
	Erdur ^[18]	20	6.06 ± 0.29	3.89 ± 0.34	-	0.001
0-4 months	Tehranchi ^[20]	8	6.65 ± 0.83	6.76 ± 0.76	-	0.006
0-5 months	Zeitounlouian ^[15]	21	3.90 ± 1.36	3.94 ± 1.12	(-0.83, 0.75)	0.918

PRF: platelet-rich rich fibrin

表4 PRF对正畸牙移动率的影响

Table 4 Effect of PRF on orthodontic tooth movement rate

 $\bar{x} \pm s$

Overall time/month	Study	<i>n</i>	PRF group	Control group	Mean difference (95% CI)	<i>P</i>
0-1	Karakasli ^[17]	40	0.50 ± 0.11	0.30 ± 0.06	-	0.001
	Zeitounlouian ^[15]	21	0.92 ± 0.56	1.25 ± 0.99	-0.33 (-0.80, 0.13)	0.157
1-2	Erdur ^[18]	20	1.90 ± 0.10	1.23 ± 0.12	-	0.001
	Zeitounlouian ^[15]	21	1.40 ± 0.83	0.97 ± 0.61	0.43 (0.08, 0.78)	0.018
2-3	Erdur ^[18]	20	1.88 ± 0.11	1.23 ± 0.13	-	0.001
	Zeitounlouian ^[15]	21	1.46 ± 0.56	1.13 ± 0.60	0.33 (-0.02, 0.68)	0.067
3-4	Zeitounlouian ^[15]	21	1.14 ± 0.87	0.86 ± 0.71	0.28 (-0.72, 1.27)	0.533
4-5	Zeitounlouian ^[15]	21	0.68 ± 0.55	1.23 ± 0.13	-0.55 (-1.39, 1.04)	0.299

PRF: platelet-rich rich fibrin

次使用PRF超过4个月后,PRF会失去促进牙齿移动的作用,甚至还会抑制牙齿移动。因此,有研究提出多次使用PRF来改善其长期作用的观点^[15, 29],但如何最有效地使用“加强针”还有待进一步研究。PRF效应的时序性变化可能与PRF因子的特殊生物作用和人体的负反馈调节机制有关^[30-31]。

综上所述,在正畸中使用PRF,前期能促进牙齿移动,而其长期作用仍有待探究。纳入研究的样本量、PRF制备和使用方法、结局测量方法等都会对异质性产生影响,使结果、结论分析产生误差。因此,关于PRF对正畸牙移动的确切影响,仍需开展大规模、长时间、具有统一标准的PRF操作方法的随机对照试验。

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