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·基础研究·

富血小板纤维蛋白与脱细胞真皮基质修复兔口腔黏膜缺损效果比较

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【摘要】　目的　探讨富血小板纤维蛋白（platelet rich fibrin，PRF）和脱细胞真皮基质（acellular dermal matrix，ADM）对口腔黏膜缺损修复的效果，为口腔种植手术中实现软组织增量提供实验依据。**方法**　将36只健康日本雄性大耳兔随机分为PRF组，ADM组，Autograft组（自体结缔组织移植组）及Control组（空白对照组），每组9只，在兔硬腭距上颌门齿8 mm的中间位置制备10 mm标准黏膜缺损。ADM组、PRF组及Autograft组分别植入ADM、自体PRF以及自体黏膜，Control组对创面行纱布按压处理；分别于术后7、14、21 d进行创面愈合率观察，并于术区取材后行HE染色，观察其炎症等级和上皮平均厚度，并对结果进行统计分析。**结果**　随着时间的增加，PRF组、ADM组、Autograft组分别与Control组相比，可观察到显著促进创面的愈合（$P < 0.05$）；PRF组与ADM组相比在任一时间点创面愈合程度无显著差异（$P > 0.05$）；PRF组、ADM组各时间点创面愈合程度均比Autograft组较低（$P < 0.05$）。HE染色结果显示，与Control组相比，PRF组、ADM组和Autograft组的炎症等级均有减轻，差异具有统计学意义（$P < 0.05$）；而PRF组、ADM组与Autograft组两两相比，炎症等级无显著差异（$P > 0.05$）。ADM组与Autograft组相比，上皮厚度无显著差异（$P > 0.05$）；ADM组与PRF组比较，在7 d和14 d时ADM组的上皮厚度更高（$P < 0.05$），而在21 d时两者无显著性差异（$P > 0.05$）。**结论**　PRF与ADM用于口腔黏膜缺损修复，创面愈合效果相似，均可作为代替结缔组织移植的软组织增量材料。

【关键词】　脱细胞真皮基质；　富血小板纤维蛋白；　自体结缔组织移植；　口腔黏膜缺损；　牙种植；　创面愈合率；　炎症等级；　上皮厚度；　动物实验
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Comparison of platelet rich fibrin and acellular dermal matrix in repairing rabbits′ oral mucosal defects

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【Abstract】　Objective　To investigate the effects of platelet-rich fibrin (PRF) and acellular dermal matrix (ADM) on the repair of oral mucosal defects and to provide the basis for soft tissue growth in oral implant operations. **Methods**　Thirty-six healthy male Japanese big ear rabbits were randomly divided into the PRF group，ADM group，Autograft group (autologous connective tissue transplantation group) and Control group (blank control group)；each group contained nine rabbits. Between the midline and the hard palate maxillary incisors，in an 8-mm location preparation and a 10-mm standard mucosa defect，the ADM group，PRF and Autograft group were implanted with ADM，autologous PRF and autologous cornification mucosa，respectively，whereas the control group had wound gauze compression processing

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at 7, 14, and 21 days to determine the wound healing rate in the area selected by HE staining. The inflammatory grade and average epithelial thickness were observed, and the results were statistically analyzed. **Results** Compared with the control group, the PRF, ADM and Autograft groups had significantly advanced wound healing ($P < 0.05$). The wound healing degree in the PRF group was similar to that of the ADM group at all time points ($P > 0.05$). The wound healing degree in the PRF and ADM groups was lower than that of the Autograft group at each time point ($P < 0.05$). HE staining results showed that compared with the control group, the levels of inflammation in the PRF group, ADM group and Autograft group were reduced, and the difference was statistically significant ($P < 0.05$). Nevertheless, there was no significant difference between the PRF, ADM and Autograft groups ($P > 0.05$). The epithelial thickness in the ADM group was similar to that in the Autograft group ($P > 0.05$). The epithelial thickness in the ADM group was higher than that in the PRF group at 7 d and 14 d ($P < 0.05$), but there was no significant difference at 21 d ($P > 0.05$). **Conclusion** PRF and ADM have similar healing effects in repairing oral mucosa defects, and they can be used as soft tissue augmentation materials instead of connective tissue transplantation.

【Key words】 acellular dermal matrix; platelet rich fibrin; autologous connective tissue transplantation; oral mucosa defect; dental implant; wound healing rate; inflammation level; epithelial thickness; animal experiment
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随着对口腔种植技术的深入研究，研究者发现当种植术区具有充足的软组织量时才能保证良好的生物学封闭，减少种植体周围炎的发生[1]。目前，修复口腔黏膜缺损的方法有很多，然而判断软组织增量效果的金标准仍然是自体结缔组织移植[2]，但其创伤较大、易发生感染且需要开辟第二术区，不易被患者接受。随着生物科技的进步和发展，生物膜性材料逐步发展并成为临床中常用的软组织修复材料，其中富血小板纤维蛋白（platelet rich fibrin，PRF）和脱细胞真皮基质（acellular dermal matrix，ADM）在临床上应用较多，但目前两种修复材料增量技术比较相关研究较少[3]。本实验主要探讨PRF和ADM对口腔黏膜缺损的修复效果，为生物膜性材料在口腔种植中的临床应用提供依据。

1　材料与方法

1.1　实验动物

3月龄健康雄性日本大耳白兔36只，体重2.74～3.08 kg，由太原市小店区丰泽园种养农民专业合作社提供，实验动物生产许可证号SCXK（晋）2015-0003。

1.2　实验分组

随机将实验动物分为4组，每组9只；分别为PRF组，ADM组，Autograft组（自体结缔组织移植组）及Control组（空白对照组）。本研究已获得山西医科大学伦理委员会批准。

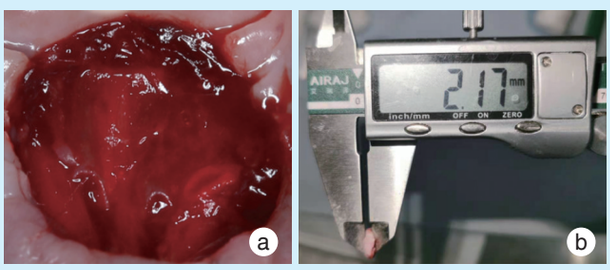
1.3　PRF及ADM的获取

对PRF组9只兔子在耳中动脉处连接真空采血管，采血量为5 mL，以3 000 rpm转速离心10 min。静置后，取出并修剪PRF凝胶，最后用纱布挤压法除去PRF凝胶中的水分，塑形成PRF膜。ADM组采用吉特瑞®医用胶原修复膜，修剪为直径10 mm的圆形膜。

1.4　制备10 mm黏膜缺损模型以及缺损平均厚度的测定

术前8 h对实验动物禁饮食，使用苯巴比妥钠（100 mg/kg）经腹腔注射实施麻醉，待麻醉后固定于兔台。1%碘伏消毒，铺单，拉开口角，暴露硬腭。在距上颌门齿8 mm的硬腭区中央位置，用直径为10 mm环形切取器制备黏膜缺损，去除黏骨膜瓣形成圆形缺损区（图1a），暴露骨面。PRF组用4-0丝线将对应的PRF间断缝合于各自的黏膜缺损处；ADM组用4-0丝线将直径10 mm的ADM间断缝合于各自的黏膜缺损处；Autograft组在术区后方2.5 mm处开辟第二术区，用10 mm环形切取器取结缔组织瓣，修剪后间断缝合于各自的黏膜缺损处，第二术区纱布压迫30 min止血；Control组黏膜缺损处使用纱布压迫30 min止血。术前1 h和术后连续3 d肌肉注射青霉素钠（100 000 U/kg），

1次/d，预防感染。游标卡尺测量在建模时切取下的硬腭黏膜中心及外侧，取平均值作为各组的硬腭黏膜厚度（图1b）。



a: 10 mm mucosal defect model; b: determination of mean thickness of mucosal defect

Figure 1　Preparation of 10 mm mucosal defect model and measurement of mucosal defect thickness

图1　制备10 mm黏膜缺损模型及测量黏膜缺损厚度

1.5　效果评价

1.5.1　创面愈合率的测定　术后7、14、21 d将四组的实验兔麻醉后肉眼观察创面愈合情况并拍照记录。观察完毕后各组随机处死3只，利用牙周探针给定标准长度，单反相机垂直与组织创面进行拍摄。ImagePlus 6.0软件测量愈合率。$R=(S_{初}-S_{末})\div S_{初}$。R为愈合率，$S_{初}$为初始创面面积，$S_{末}$为未愈合的创面面积。创面愈合区组织标本行石蜡包埋切片。

1.5.2　炎症等级的评分　在100倍及400倍显微镜下观察各组织HE切片组织，并给予炎症等级评分测定。0分：无炎症，或有散在炎细胞；1分：少量（<30%）炎细胞浸润；2分：介于1和3分之间；3分：大量（>60%）炎细胞浸润。具体评分标准见表1。

表1　炎症分级评分标准[4]

Table 1　Inflammation grading score criteria[4]

Classification	Microscopic description	Grade
–	Basic normal, inflammatory cells occasional or absent	0
+	Small number of inflammatory cells infiltrate	1
++	Between + and +++	2
+++	Large, diffuse infiltration of inflammatory cells with multinucleated giant cells forming an inflammatory granulomatous lesion	3

Small number of inflammatory cells: less than 30% total inflammatory cells; large number of inflammatory cells: more than 60% total inflammatory cells

1.5.3　上皮平均厚度测定　在100倍显微镜下采集各组织HE切片组织的5幅图像。每张图像在10个不同部位用Imageplus6.0软件测量上皮厚度，得到平均值。

1.6　统计学方法

用SPSS 24.0软件，对所有检测指标进行统计分析。计数资料用频数表示，计量资料用均数±标准差表示。炎症等级评分采用Kruskal-Wallis检验和Mann-Whitney U检验；愈合率、上皮平均厚度采用单因素方差分析和析因设计方差分析；若总体方差齐，用Bonferroni检验进行组间两两比较；若总体方差不齐，则采用Games-Howell检验。检验水准为$\alpha=0.05$。

2　结　果

2.1　黏膜缺损平均厚度

PRF组黏膜缺损平均厚度为（2.28±0.29）mm，ADM组为（2.21±0.53）mm，Autograft组为（2.18±0.16）mm，Control组为（2.26±0.20）mm；经SNK检验，$F=0.13$，$P=0.93$，各组黏膜缺损平均厚度差异无统计学意义（$P>0.05$），具有可比性，可以进行后续实验。

2.2　创面愈合率

经Bonferroni校正的多重比较结果显示：①PRF组、ADM组与Autograft组各时间点的创面愈合率均高于Control组，差异均具有统计学意义（$P<0.05$）；②PRF组与ADM组在各时间点的创面愈合率比较无显著差异（$P>0.05$）；③PRF组、ADM组在各时间点的创面愈合率均低于Autograft组，差异均具有统计学意义（PRF组：$P_{7\,d}<0.001$，$P_{14\,d}<0.001$，$P_{21\,d}<0.001$；ADM组：$P_{7\,d}<0.001$，$P_{14\,d}<0.001$，$P_{21\,d}<0.001$）。见表2、图2。

2.3　HE染色结果

将建模时切取的硬腭黏膜做HE染色，能在显微镜下看到硬腭黏膜的全部组织结构，可以认为缺损处无黏骨膜附着，完整切取了硬腭黏骨膜，可

表2　各组创面愈合率比较

Table 2　Comparison of wound healing rate in each group

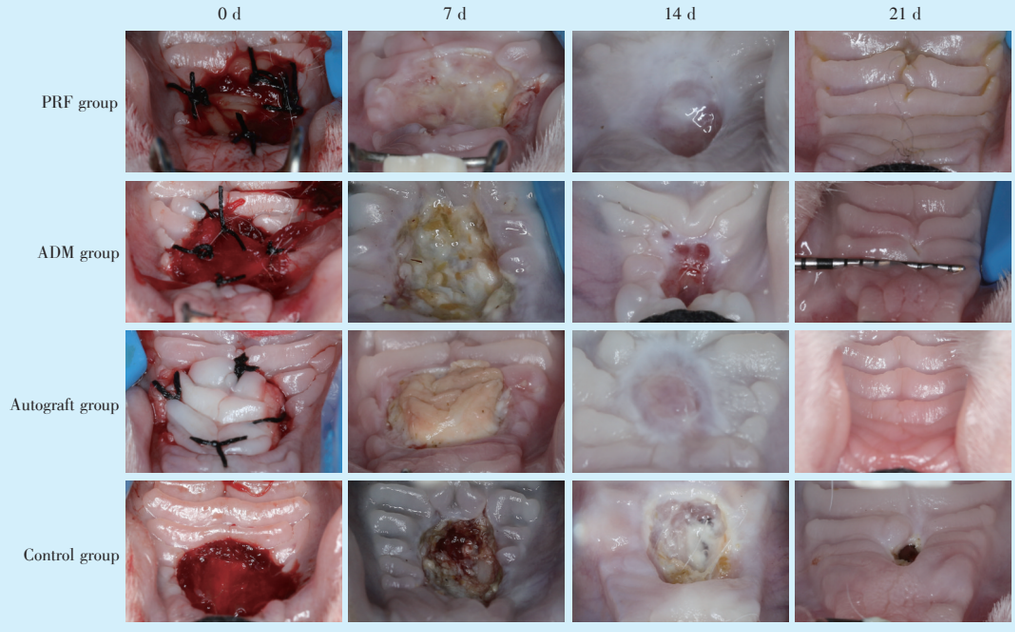
$\bar{x} \pm s$, n=3

Group	Wound healing rate(%)		
	7 d	14 d	21 d
PRF	66.13 ± 2.36#*	87.63 ± 2.20#*	97.06 ± 0.73#*
ADM	64.43 ± 2.85*#	86.56 ± 1.13*#	95.40 ± 1.21*#
Autograft	89.06 ± 3.80#△	99.16 ± 0.76#△	99.83 ± 0.28#△
Control	29.63 ± 2.31	65.23 ± 2.90	89.03 ± 1.38
F	215.047	158.569	62.636
P	< 0.001	< 0.001	< 0.001

#: compared with Control group, P <0.05; *: compared with Autograft group, P < 0.05; △: compared with ADM group, P < 0.05; PRF: platelet rich fibrin; ADM: acellular dermal matrix; Autograft: autologous connective tissue transplantation; Control: blank control

以进行后续实验。

术后7 d：Control组可见组织内大量炎性细胞浸润，组织结构紊乱，新生血管较少；其余三组细胞开始修复，可见结缔组织增值，可见新生毛细血管，炎性细胞数量较Control组少；ADM组结缔组织排列更为规则、致密（与ADM本身的结缔组织网状结构有关系）；Autograft仍有上皮钉突存在。术后14 d：Control组上皮开始修复，但多处组织仍有大量炎性细胞浸润；Autograft组上皮呈现完整连续状态；PRF组与ADM组仍有新生肉芽组织向表面生长，上皮不完全连续，且ADM组上皮与PRF组相比较厚。术后21 d：Control组炎症减轻，其余三组上皮完整，且厚度基本一致。见图3。



The wound healing process in each group was observed. It was found that 21 days after the operation, the wound in the PRF group was basically healed. Only part of the plica could not be completely closed. There were still small wounds in the ADM group that could not be healed. The wounds in the Autograft group were completely healed, whereas the wounds in the Control group were poorly healed, and there were still large wounds; PRF: platelet rich fibrin; ADM: acellular dermal matrix; Autograft: autologous connective tissue transplantation; Control: blank control

Figure 2　Wound healing of hard palate mucosal defects in each group

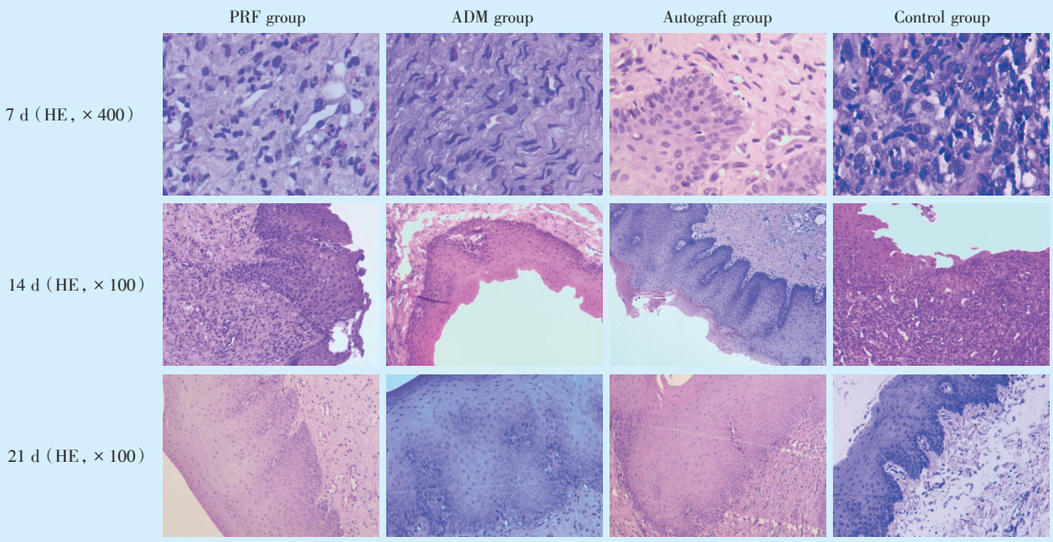
图2　各组硬腭黏膜缺损术后创面愈合情况

2.4　炎症等级评分

Bonferroni校正的Mann-Whitney U检验结果显示，①PRF组、ADM组、Autograft组分别与Control组在术后各时间点的炎症等级评分比较，差异均具有统计学意义（P<0.05）；②PRF组、ADM组与Autograft组在术后各时间点的炎症等级评分两两之间比较，差异均无统计学意义（P>0.05）。见表3。

2.5　上皮厚度

经Bonferroni校正的多重比较结果显示：①PRF组、ADM组与Autograft组在术后各时间点的上皮厚度均比Control组高（P < 0.05）；②ADM组在术后7、14 d的上皮厚度比PRF组高，差异均具有统



At 7 days after the operation, the connective tissue of the ADM group was more regular and denser than that of the other groups. At 14 days after the operation, the epithelial thickness in the ADM and Autograft groups was close to but greater than that of the PRF group. At 21 days after the operation, the epithelial thicknesses in the PRF, ADM and Autograft groups were similar, and all of them were larger than that of the Control group. PRF: platelet-rich fibrin; ADM: acellular dermal matrix; Autograft: autologous connective tissue transplantation; Control: blank control

Figure 3　HE staining of hard palate mucosa in each group after operation

图3　各组硬腭黏膜术后HE染色

表3　各组炎症等级评分

Table 3　Inflammation grade score of each group　n=3

Group		Inflammation grade score			
		0	1	2	3
PRF	7 d	0	0	3	0
	14 d	0	1	2	0
	21 d	1	1	1	0
ADM	7 d	0	0	3	0
	14 d	0	1	2	0
	21 d	0	2	1	0
Autograft	7 d	1	1	1	0
	14 d	1	2	0	0
	21 d	3	0	0	0
Control	7 d	0	0	0	3
	14 d	0	1	1	1
	21 d	0	1	2	0

PRF: platelet rich fibrin; ADM: acellular dermal matrix; Autograft: autologous connective tissue transplantation; Control: blank control

计学意义($P_{7\,d}$ < 0.001, $P_{14\,d}$ < 0.001)；③ADM组在术后各时间点的上皮厚度与Autograft组相比无显著差异(P > 0.05)；④PRF组在术后7、14 d的上皮厚度均低于Autograft组，差异具有统计学意义($P_{7\,d}$ < 0.001, $P_{14\,d}$ < 0.001)。见表4。

表4　各组术后上皮厚度比较

Table 4　Comparison of postoperative epithelial thickness in each group　$\bar{x} \pm s$, n=3

Group	Epithelial thickness (μm)		
	7 d	14 d	21 d
PRF	129.33 ± 17.84$^{\#*\triangle}$	221.20 ± 18.31$^{\#*\triangle}$	278.13 ± 8.29$^{\#}$
ADM	189.77 ± 7.13$^{\#}$	292.10 ± 20.09$^{\#}$	280.67 ± 6.45$^{\#}$
Autograft	192.60 ± 10.93$^{\#}$	316.30 ± 21.51$^{\#}$	291.33 ± 1.65$^{\#}$
Control	0	129.37 ± 14.43	232.07 ± 10.00
F	154.58	59.96	38.68
P	< 0.001	< 0.001	< 0.001

#: compared with Control group, P < 0.05; *: compared with Autograft group, P < 0.05; △: compared with ADM group, P < 0.05; PRF: platelet rich fibrin; ADM: acellular dermal matrix; Autograft: autologous connective tissue transplantation; Control: blank control

3　讨　论

本实验选择兔作为实验对象，主要考虑以下原因：①兔硬腭咀嚼黏膜相对充足，且组织学结构与人的口腔黏膜类似；②对于兔来说10 mL采血量被认为是安全可行的，满足本次实验制备PRF的采血要求。对实验动物制备软组织缺损目前国内外无明确统一的标准。本实验应用10 mm的标准

化器械，可认为是具有科学性、重复性、可靠性、标准化口腔软组织缺损动物模型，符合实验的条件，可以保证实验的顺利进行[5]。

PRF是以富血小板血浆（platelet rich plasma，PRP）为基础研制的新一代血小板浓缩制品，是自体全血离心的产物，被认为是一种自体移植物[6]。收集自体血立即3 000 rpm离心10 min，可得到去血小板血浆、PRF凝胶和红细胞碎片，其分别位于离心管的上、中、下层；制备过程不添加抗凝剂和外部化学物质。PRF疏松的结构能够容纳大量的血小板及生长因子，如血管内皮细胞生长因子（vascular endothelial growth factor，VEGF）、表皮生长因子（epidermal growth factor，EGF）、转化生长因子（transforming growth factor-β，TGF-β）和血小板衍生生长因子（platelet derived growth factor，PDGF）等。在这些生长因子的作用下，软组织愈合和成熟的三个关键步骤（血管生成、免疫和上皮覆盖）可以被同时支持，从而大大加快软组织的愈合[7]，因PRF的以上特性，其被应用于众多领域中。在外科手术中，PRF的应用可加速愈合，减少不良反应并改善预后[8]。PRF被证实可以促进成纤维细胞增殖和创面愈合[9]。在口腔医学中，PRF已被证实能够促进牙龈成纤维细胞的黏附、迁移及增殖，还能在愈合过程中高效地表达Ⅰ型胶原蛋白[10]。近些年来，随着对PRF制备流程的改良，又成功制取出了i-PRF（injectable platelet rich fibrin，i-PRF）等基于PRF的衍生物，其可以更加有效且长期的释放生长因子，进一步加快了软组织的愈合[11]。

ADM是通过特殊处理，去除了所有细胞成分的一种组织移植物。由于这些机械加工的生物支架能快速结合到生物组织中，因此被广泛应用于各种外科手术中，且已被提议作为治疗口腔黏膜创伤的一种方法。ADM处理过程为去除含角蛋白的表皮后，处理真皮层以去除所有的脱氧核糖核酸，而不破坏胶原基质，故ADM具有充分的空间供宿主细胞浸润、促进新生血管形成和加速上皮形成[12]。Xu等[13]的动物实验结果显示ADM对于兔硬腭软组织缺损可刺激轻微的炎症反应，表现出快速的上皮化和血管重建，并伴有VEGF和葡萄糖转运蛋白（glucose transporter type 1，GLUT1）的增加，促进缺损部位的组织生长。无论是在牙周整形或是口腔种植手术中，ADM都显示出了与结缔组织移植物（connective tissue graft，CTG）相当的牙龈退缩减少和软组织厚度增加，而且能获得与CTG相同的舒适度[14]。目前国外对ADM的使用较为广泛，应用于众多领域，如外科、乳腺外科、烧伤整形科等；在口腔治疗中应用于颌面外科、牙周科、口腔种植科等。然而在国内，ADM仍未被广泛使用，在口腔治疗中仅被应用于牙周手术，充当上皮下结缔组织瓣[15]。

在本实验中，笔者比较了ADM、PRF和自体结缔组织移植物对黏膜缺损的修复效果，结果显示，与PRF相比，ADM在术后2周以内的上皮厚度增量方面更具有优势，但在3周后，PRF与ADM的上皮厚度增量效果无显著差异。ADM对上皮厚度增量的影响主要涉及以下机制：①ADM具有的纤维三维网状结构，能够起调节、诱导、促进作用，为宿主成纤维细胞、血管内皮细胞等的和增生提供网状空间，局部形成新生血管和上皮，容纳并支撑细胞的生长；②PRF降解期为2～3周，而ADM在体内可存在数月，更有利于萎缩组织的再生，更适合应用于牙周科对于牙龈退缩的治疗；③ADM可以和人体结缔组织实现整合，有利于ADM的固定。

本实验结果显示，ADM可以获得与CTG接近的软组织增量效果。但是ADM仍然存在不足之处：①虽然有证据表明ADM移植可以取得与CTG相似的结果[16]，但是最近的一项长达15年的临床研究结果显示，尽管ADM长期的美学效果较优，但效果并不如结缔组织移植物稳定，存在少量的组织萎缩[17]；②在创面愈合初期，ADM组与血液提取物组相比CD68阳性细胞较少，且CD31染色显示创口边缘处新生血管较少[18]；③ADM组与宿主自生的结缔组织仍有差异，在ADM内可观察到毛细血管和小血管[19]；④ADM很难完全去除所有细胞残余物。随着技术的不断改善，新的方法不断应用到ADM的制备中，ADM的安全性在不断提高，但其仍有疾病传播的理论风险，这是所有异体移植制剂都存在的问题。

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