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· 临床研究 ·

浓缩生长因子联合脱蛋白牛骨基质位点保存效果的临床及组织学评价

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【摘要】 目的 从临床及组织形态计量学角度评价浓缩生长因子(concentrated growth factor, CGF)联合脱蛋白牛骨基质(deproteinated bovine bone mineral, DBBM)在拔牙位点保存中成骨效果。**方法** 选取需拔除患牙并接受位点保存后延期种植的26例患者为研究对象,采用随机数字表法将患者分为DBBM组和CGF+DBBM组,每组13例。DBBM组拔牙后同期植入DBBM, CGF+DBBM组拔牙后同期植入CGF+DBBM,两组均覆盖Bio-Gide胶原膜。术前、术后6个月分别拍摄CBCT以测量牙槽骨高度、宽度的变化,并于位点保存术后6个月种植术中钻取骨标本进行组织学观察和组织形态计量学分析。**结果** 影像学结果显示CGF+DBBM组和DBBM组位点保存术后6个月牙槽骨高度和宽度均发生吸收,CGF+DBBM组牙槽嵴宽度吸收少于DBBM组,且差异具有统计学意义($P < 0.05$);组织形态计量学结果显示CGF+DBBM组和DBBM组新生骨平均面积百分比分别为 $(35.30 \pm 3.56)\%$ 、 $(26.38 \pm 5.04)\%$, CGF+DBBM组新生骨量优于DBBM组,且差异具有统计学意义($P < 0.05$)。**结论** CGF联合骨替代材料DBBM可以更有效地维持拔牙后牙槽骨体积、形态,其成骨效果优于DBBM单一材料的应用,可为种植修复创造有利条件。

【关键词】 牙种植; 位点保存; 骨替代材料; 脱蛋白牛骨基质; Bio-Oss; Bio-Gide胶原膜; 引导骨再生; 浓缩生长因子; 新生骨; 组织形态计量学

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【Abstract】 Objective To evaluate the osteogenic effect of concentrated growth factor (CGF) combined with deproteinated bovine bone mineral (DBBM) in site preservation using clinical and histomorphometric observations. **Methods** A total of 26 patients who needed extraction of affected teeth and received staged implantation after site preservation were selected. The patients were randomly divided into the DBBM group (Bio-Oss was implanted simultaneously after extraction) and CGF+DBBM group (CGF+Bio-Oss was implanted simultaneously after extraction), with 13 patients in each group, and both groups were covered with Bio-Gide collagen membrane. Cone beam computed tomography (CBCT) was performed preoperatively and 6 months later to measure the changes in alveolar bone height and width, and the bone specimens were drilled 6 months after site preservation during implant surgery for histological analyses. **Results**

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CBCT showed that the height and width of alveolar bone were absorbed 6 months after site preservation in the CGF+DBBM and DBBM groups, and the reduction in alveolar ridge width in the CGF+DBBM group was statistically less than the DBBM group ($P < 0.05$). The histomorphometry results showed that the percentage of new bone in the CGF+DBBM and DBBM groups were $35.30\% \pm 3.56\%$ and $26.38\% \pm 5.04\%$, respectively, and the amount of new bone in the CGF+DBBM group was statistically higher than the DBBM group ($P < 0.05$). **Conclusion** CGF combined with DBBM is superior to DBBM in maintaining the alveolar bone volume and shape in site preservation, which creates favorable conditions for implant restoration.

【Key words】 dental implantation; site preservation; bone substitute; deproteinated bovine bone mineral; Bio-Oss; Bio-Gide collagen membrane; guided bone regeneration; concentrated growth factor; new bone; histomorphometry

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健康充足的骨组织对获得种植体的初期稳定性十分重要,而良好的初期稳定性是实现骨结合的必要前提。为避免延期种植面临的骨吸收问题,2001年,Paolantonio等^[1]提出即刻种植可能抵消拔牙后牙槽嵴吸收的设想,而Araújo等^[2]的动物实验和Sanz等^[3]的人体研究发现即刻种植仅促进拔牙位点骨组织改建,并不能预防骨壁的吸收。骨劈开、Onlay植骨等骨增量手术程序繁琐、术后并发症较多,大都旨在修复牙槽骨吸收造成的骨缺损,无法从根源上减少牙槽骨吸收。因此,位点保存又称为牙槽嵴保存(alveolar ridge preservation, ARP)成为国内外研究热点^[4-5]。诸研究从影像学角度表明^[6-7],位点保存可以有效地维持牙槽骨体积、形态,具有临床应用价值,但缺少人体组织学及组织形态计量学数据支持。本研究应用浓缩生长因子(concentrated growth factor, CGF)联合脱蛋白牛骨基质(deproteinated bovine bone mineral, DBBM)同时发挥骨引导和骨诱导双重优势进行位点保存,从组织形态计量学、影像学即“质”与“量”双重角度评价成骨效果,以期有位点保存提供一定的临床依据。

1 资料和方法

1.1 病例资料

选取2020年1月至2021年4月于浙江省人民医院口腔医学中心就诊需拔除单根牙并接受种植修复的患者26例,年龄范围20~45岁,平均年龄(30 ± 2.56)岁。其中男性14例(14颗牙),女性12例(12颗牙),将纳入研究的26颗患牙随机分为2组:DBBM组(对照组)13例,男性5例,女性8例

(前牙4颗,前磨牙9颗);CGF+DBBM组(试验组)13例,男性9例,女性4例(前牙6颗,前磨牙7颗);2组在性别、年龄、骨缺损类型方面差异无统计学意义($P > 0.05$)。

纳入标准:①年满18周岁因龋病、牙外伤、根尖周病等拔除患牙并接受种植修复的患者;②存在相邻的(近中和/或远中)天然牙齿;③术前CBCT显示拔牙位点骨壁完整;④无全身系统性疾病且每天吸烟不超过10支;⑤患者依从性好。

排除标准:①未受控制的糖尿病(糖化血红蛋白 $> 7\%$)、骨质疏松症或任何其他可能影响术后愈合的局部或全身性疾病;②接受放疗和(或)化疗的恶性肿瘤病患者;③怀孕或处于哺乳期的女性患者;④服用某些药物(如类固醇、双膦酸盐等)的患者;⑤患者难以配合术后随访。

本研究经浙江省人民医院伦理委员会批准(审批号:2017KY049),患者均自愿参加本研究,并签署知情同意书,本研究临床试验注册号(浙江省人民医院:2017KY049)。

1.2 仪器设备及材料

CBCT(Promax 3D, Planmeca, 芬兰)、Medifuge离心加速器(2002-30, Silfradent, 意大利)、微创挺(Helmut Zepf, 英国)、DBBM(Bio-Oss, 0.25 g, Geistlich, 瑞士)、Bio-Gide生物膜(25 mm × 25 mm, Geistlich, 瑞士)、静脉真空负压采血管(江苏宇力医疗器械有限公司)、取骨钻(3 mm × 8 mm, Meisinger, 德国)、光学显微镜(Nikon, 日本)。

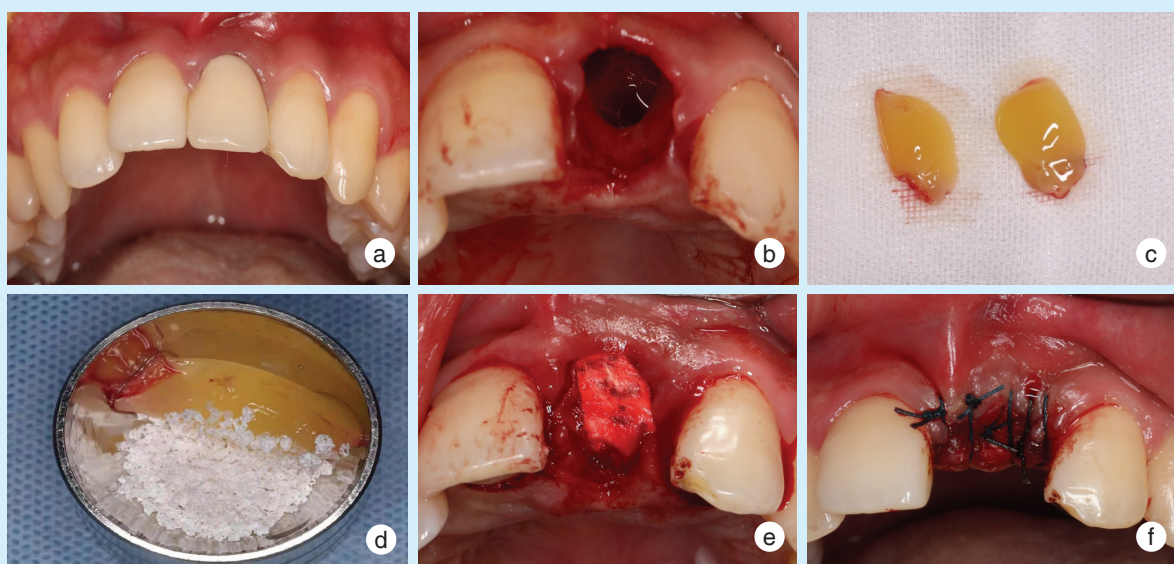
1.3 手术方法

1.3.1 术前准备 所有患者拔牙术前均接受牙周

基础治疗,给予维护口腔卫生指导。

1.3.2 CGF+DBBM组行拔牙位点保存术 ①CGF制备:术前从患者上臂抽取10 mL静脉血,置入真空采血管,随即放入变速离心机,设定制备CGF程序离心12 min。离心结束后试管内血液分为三层:最上层为贫血小板血浆(platelet poor plasma, PPP),中间层为凝胶状纤维蛋白即CGF,最下层为红细胞及血小板。倒出上层血清,将中间层CGF取出存储备用。②微创拔牙:患者术前30 min口

服抗生素,0.12%复方氯己定溶液含漱1 min。常规消毒铺巾,局部麻醉下微创拔牙,尽量保证患牙(唇)颊侧和(腭)舌侧牙槽骨骨壁的完整性,降低对软、硬组织的损伤。拔除患牙后,彻底搔刮牙槽窝,去净炎性肉芽、根尖周囊肿等感染组织至新鲜创面,生理盐水反复冲洗。③植入材料:使用眼科剪将CGF凝块剪碎并与Bio-Oss骨粉充分混合,分层充填至牙槽嵴顶,表面覆盖Bio-Gide膜,龈骨膜瓣减张,采用4-0不可吸收缝线封闭拔牙窝(图1)。



a: labial view of the left upper central incisor before tooth extraction; b: socket after surgical debridement; c: CGF obtained via centrifugation; d: mixed CGF with Bio-Oss; e: the socket was filled and covered with the Bio-Gide membrane; f: labial view of the left upper central incisor after suture. CGF: concentrated growth factor; DBBM: deproteinized bovine bone mineral

Figure 1 Site preservation surgical procedures of the CGF+DBBM group

图1 CGF+DBBM组位点保存手术过程

1.3.3 DBBM组行拔牙位点保存术 ①微创拔牙:步骤同1.3.2;②植入材料:拔牙窝内分层充填Bio-Oss骨粉至牙槽嵴顶,表面覆盖Bio-Gide胶原膜,龈骨膜瓣减张,采用4-0不可吸收缝线封闭拔牙窝。

1.3.4 术后医嘱 所有患者术后3~5 d口服抗生素预防感染,0.12%氯己定溶液含漱以维护口腔卫生,术后10 d拆除术区缝合线。

1.3.5 术后6个月种植手术 ①种植术前拍摄CBCT评估拔牙窝愈合状况;②手术流程:常规消毒铺巾,局部麻醉下于种植位点牙槽嵴顶作水平切口,翻开黏骨膜瓣显露骨面,使用内径2.8 mm取骨钻钻取高度为4~6 mm组织标本(图2),立即置入装有4%缓冲福尔马林的单独容器中。取材后

种植术区逐级备洞,植入相应型号种植体,安置覆盖螺丝,间断缝合创口。若种植术中发生骨开窗或骨开裂,则进行引导骨组织再生术(guided bone regeneration, GBR)。以上操作均由同一专业口腔外科医生完成。

1.4 评价方法

1.4.1 影像学评价 所有患者于术前、术后6个月拍摄CBCT,比较组内和两组间牙槽骨高度和宽度变化。CBCT的拍摄和数据测量均由同一位经验丰富的放射科医师完成,确认每位患者前后两次测量所截取的断面及标志点均在同一位置。取拔牙位点牙槽骨正中矢状面,从(唇)颊侧牙槽嵴顶至鼻底最外侧缘的距离即为(唇)颊侧骨板高度



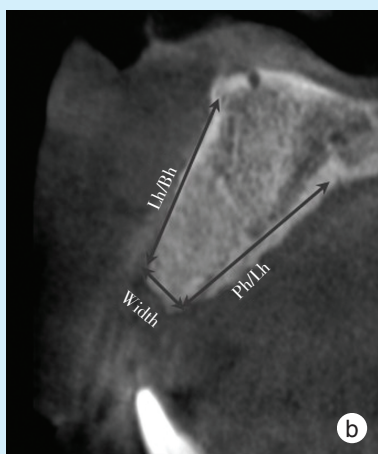
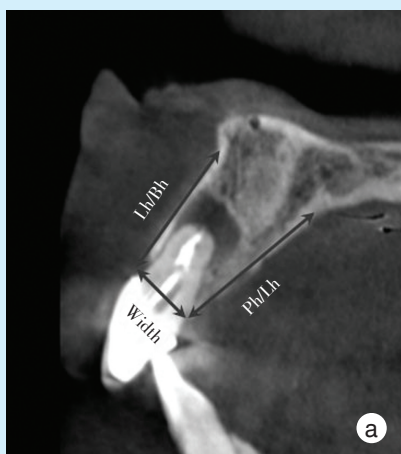
Diameter 2.8 mm × height 4 mm

Figure 2 Cylindrical bone tissue specimen

图2 圆柱状骨组织标本

(labial/buccal-height, Lh/Bh), 从(腭)舌侧牙槽嵴顶至上颌骨腭突转折处的距离即为(腭)舌侧骨板高

度(palatal/lingual-height, Ph/Lh), (唇)颊侧与(腭)舌侧牙槽嵴顶的连线即为骨宽度(width)(图3)。



a: before site preservation; b: 6 months after site preservation; CBCT: cone beam computed tomography; Lh/Bh: labial/buccal-height; Ph/Lh: palatal/lingual-height

Figure 3 Measurement method on CBCT image

图3 CBCT影像测量方法

1.4.2 组织学评价 取材样本均置入装有4%缓冲福尔马林液体的单独容器中固定24 h, 随后在10%甲酸中脱钙3 d并进行酒精梯度脱水, 石蜡包埋, 最后沿取材样本纵轴连续切片, 厚度约5 μ m, 行HE染色。取样本最中央的1~2个切片, 分别在40、100、400放大倍数下进行组织学观察, 采集同一放大倍数($\times 40$)图像, 使用IPP 6.0软件分析新生骨百分比。

1.5 统计学分析

采用SPSS 21.0软件对所测数据进行统计学分析, 计量资料以均数 $\pm$ 标准差表示。配对样本 t 检验进行组内试验前后比较, 两独立样本 t 检验进行组间比较, $P < 0.05$ 被认为差异具有统计学意义。

2 结果

本研究有26例患者符合纳入标准, 共26颗单根牙(前牙10颗, 前磨牙16颗)。所有患者均符合随访方案, 术后10 d拆线进行随访评估显示, 软组织愈合良好, 无炎症迹象。

愈合良好, 无炎症迹象。

2.1 影像学比较

影像学结果显示, 与术前相比, CGF+DBBM组和DBBM组位点保存术后6个月牙槽骨高度、宽度均降低, 且差异具有统计学意义($P < 0.05$)(表1)。

CGF+DBBM组和DBBM组术后6个月牙槽骨高度变化差异无统计学意义($P > 0.05$), CGF+DBBM组牙槽嵴宽度吸收量小于DBBM组, 且差异具有统计学意义($P < 0.05$)(表2)。

2.2 组织切片观察

CGF+DBBM组(图4a~4b)大量新生骨组织(NB)紧密包绕剩余移植材料(RG), 周围可见少量纤维结缔组织(CT); 新生骨组织内见有大量骨细胞(O), 剩余移植材料内少见空骨陷窝(EL)(图4c)。

DBBM组(图4d、4e)少量新生骨组织(NB)紧密包绕剩余移植材料(RG), 周围可见大量纤维结缔组织(CT); 新生骨组织内骨细胞(O)较少, 剩余移植材料内可见大量空骨陷窝(EL)(图4f)。

表1 CGF+DBBM组与DBBM组位点保存术前与术后6个月牙槽骨高度和宽度比较

Table 1 Comparison of the ridge height and width between the CGF+DBBM group and the DBBM group before site preservation and 6 months postoperatively $\bar{x} \pm s$, mm

Groups	Items	Preoperative	6 months later	<i>t</i>	<i>P</i>
DBBM	Lh/Bh	15.47 ± 1.96	14.70 ± 1.99	8.730	< 0.001
	Ph/Lh	14.89 ± 2.05	14.46 ± 2.02	5.656	< 0.001
	Width	6.65 ± 0.97	5.63 ± 1.05	12.317	< 0.001
CGF+DBBM	Lh/Bh	15.59 ± 1.95	14.89 ± 1.87	6.565	< 0.001
	Ph/Lh	15.14 ± 2.16	14.76 ± 2.24	4.685	0.001
	Width	6.97 ± 1.03	6.00 ± 1.15	8.198	< 0.001

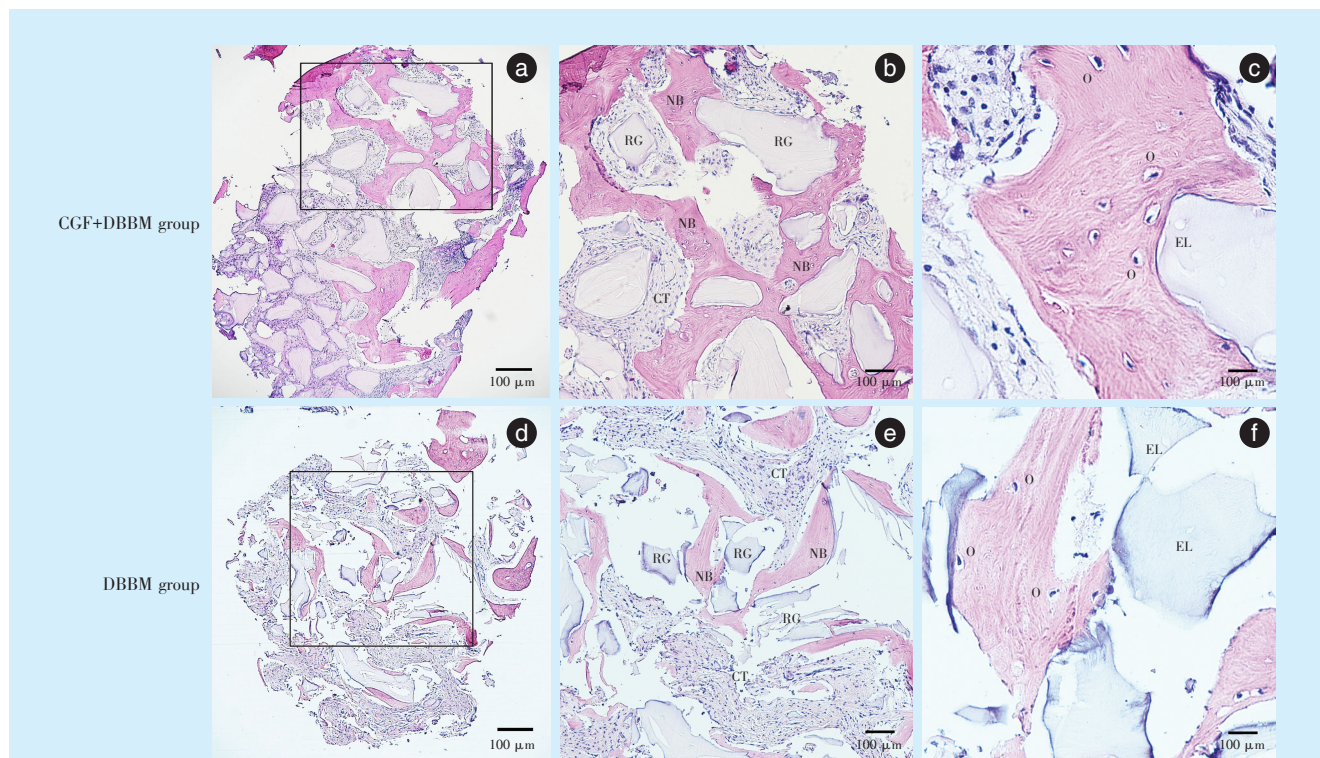
DBBM: deproteinated bovine bone mineral; CGF: concentrated growth factor; Lh/Bh: labial/buccal-height; Ph/Lh: palatal/lingual-height

表2 CGF+DBBM组与DBBM组间位点保存术后6个月牙槽骨高度和宽度变化比较

Table 2 Changes in the height and width of alveolar bone between the CGF+DBBM group and the DBBM group 6 months after site preservation $\bar{x} \pm s$, mm

Items	DBBM	CGF+DBBM	<i>t</i>	<i>P</i>
Lh/Bh	0.77 ± 0.31	0.69 ± 0.38	0.250	0.805
Ph/Lh	0.43 ± 0.27	0.37 ± 0.28	0.367	0.307
Width	1.01 ± 0.29	0.97 ± 0.42	3.259	0.003

DBBM: deproteinated bovine bone mineral; CGF: concentrated growth factor; Lh/Bh: labial/buccal-height; Ph/Lh: palatal/lingual-height



a&b: a large amount of new bone surrounded the residual graft with a minimal amount of fibrous connective tissue in the CGF+DBBM group; c: a large amount of osteocytes in NB and a minimal amount of empty lacunae in residual graft of the CGF+DBBM group. d&e: a minimal amount of new bone surrounded the residual graft with a large amount of fibrous connective tissue in the DBBM group; f: a minimal amount of osteocytes in the new bone and a large amount of empty lacunae in the residual graft of the DBBM group. CGF: concentrated growth factor; DBBM: deproteinated bovine bone mineral; NB: new bone; RG: residual graft; CT: connective tissue; O: osteocytes; EL: empty lacunae

Figure 4 Histological observation of the CGF+DBBM and DBBM groups

图4 CGF+DBBM组与DBBM组组织学观察

2.3 组织形态计量学分析

CGF+DBBM组新生骨量大于DBBM组、剩余移植材料少于DBBM组,且差异均具有统计学意义($P < 0.05$)(表3)。

表3 CGF+DBBM组与DBBM组位点保存术后6个月组织形态计量学分析

Table 3 Histomorphometric analyses of the CGF+DBBM group and the DBBM group 6 months after site preservation (%)

Group	New bone	Connective tissue	Residual graft
DBBM	26.38 ± 5.04	50.92 ± 7.37	22.76 ± 11.27
CGF+DBBM	35.30 ± 3.56	50.00 ± 6.40	14.69 ± 7.14
<i>t</i>	-5.209	0.341	2.181
<i>P</i>	< 0.001	0.736	0.039

DBBM: deproteinated bovine bone mineral; CGF: concentrated growth factor

3 讨论

骨愈合的天然基质是血凝块中的纤维蛋白,使用骨替代材料引导骨再生的机理之一是稳定血凝块,因其含有众多生长因子和细胞因子。Karageorgiou等^[8]指出大于300 μm的孔径是血管长入和后续骨化的理想尺寸,Bio-Oss(600~1 000 μm)源自小牛松质骨,较大的内部表面积及适合骨再生的交通孔隙有利于成骨细胞粘附和新生血管长入,但缺乏生长因子等活性成分,仅在骨引导作用中为成骨细胞提供黏附支架。外源性生长因子体外重组既耗时又昂贵,其安全性仍在研究中,且内源性生长因子之间复杂的相互作用无法在体外模拟,因此,如何获得丰富的内源性生长因子成为组织工程领域研究热点之一。血小板是人体自身生长因子主要来源,2006年CGF首次从人体血液中分离获得,采用差速离心技术使更多血小板被纤维蛋白捕获,内含发挥骨引导作用的纤维蛋白基质和具有骨诱导作用的生长因子,可激活血管新生,诱导和加速软组织和骨组织再生,缩短愈合时间,无交叉感染和免疫排斥风险,并具有一定的抗炎作用,在口腔种植及颌面外科等领域成为研究热点^[9],王亚敏等^[10]报道CGF应用于上颌前牙骨缺损引导骨再生取得良好效果,但CGF在位点保存中的应用效果尚缺乏深入研究。本研究从临床及组织形态计量学角度研究CGF联合Bio-Oss在拔牙位点保存中成骨效果,本研究中,拔牙窝位点保存愈合6个月后,影像学结果显示:CGF+DBBM组

(唇)颊、(腭)舌侧骨高度和牙槽嵴宽度吸收量分别为(0.69 ± 0.38)mm、(0.37 ± 0.28)mm、(0.97 ± 0.42)mm,小于DBBM组,与Barone等^[11]研究结果一致。Engler-Hamm等^[12]研究表明骨壁缺损的类型和大小影响骨修复时间。

本研究组织形态计量学分析结果显示,CGF+DBBM组新生骨、结缔组织及剩余移植材料平均面积百分比分别为(35.30 ± 3.56)%、(50.00 ± 6.40)%、(14.69 ± 7.14)%,其新生骨量高于DBBM组。Ma等^[13]在人体后牙区拔牙后即刻植入CGF凝块,术后3个月骨组织标本行Micro-CT分析显示:与自然愈合组相比,CGF组骨密度、骨体积分数、骨小梁厚度及宽度更高。组织切片观察发现CGF组成骨细胞、骨小梁数量更多,致密环层骨板发育更明显。Sohn等^[14]及Wang等^[15]分别在人体和比格犬行上颌窦提升术,术后6个月组织切片观察发现CGF联合Bio-Oss组成骨比例显著高于Bio-Oss组,且剩余移植材料颗粒更少,与本研究结果一致。

因时间有限,本研究术后只随访了6个月,且缺少自然愈合组,尽管将CGF与骨替代材料联合应用于位点保存,但牙槽骨高度和宽度仍不可避免地有所下降,这符合拔牙后牙槽骨改建的正常生理变化^[16],在今后的研究中需要深入分析种植体成功率、美学效果等各方面临床指标的差异以及生长因子与骨替代材料混合比例问题。

综上所述,CGF联合骨替代材料一定程度上维持了牙槽骨的体积和形态,生成的新生骨组织满足种植体初期稳定性需求,以期降低后期行GBR、上颌窦提升等二次骨增量手术可能性,是一种有效的种植修复前治疗方案。

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