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颅骨游离骨瓣愈合的影响因素

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摘　要

由于自体骨瓣具有良好的组织相容性、易于获取以及能够实现原位重建等优点，颅骨游离骨瓣在颅面外科及神经外科中得到了广泛应用。尽管游离骨瓣存在缺乏血供、可能被吸收的风险，但在实际临床应用中，大多数游离颅骨骨瓣能够成功生长并愈合，愈合过程受到多种因素的影响。本文旨在对游离颅骨骨瓣移植后愈合的影响因素进行文献综述。

关键词

颅骨游离骨瓣，骨愈合，骨瓣移植

Factors Influencing the Healing of Free Skull Bone Flap

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Abstract

Free cranial bone flap is widely used in craniofacial surgery and neurosurgery because of its good histocompatibility, easy access and *in situ* reconstruction. Due to the lack of blood supply, the free bone flap has the risk of absorption. However, in practical clinical application, most of the free skull bone flap can grow and heal, and the healing process is affected by various factors. In this paper, the influencing factors of healing after free cranial flap transplantation were reviewed.

Keywords

Free Skull Bone Flap, Bone Healing, Bone Flap Transplantation

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1. 引言

颅骨游离骨瓣移植是神经外科中常见的手术方式，广泛应用于颅骨缺损修复、颅骨成形术等[1]。然而，游离骨瓣的存活和愈合受到多种因素的影响，包括机械稳定性、骨膜、硬脑膜以及细胞因子等[2]。这些因素相互作用，共同决定了颅骨游离骨瓣的成活率和愈合质量。近年来，随着对颅骨愈合机制的深入研究，越来越多的证据表明，这些因素在颅骨修复过程中发挥着不可替代的作用。本文总结了机械稳定性、骨膜、硬脑膜及细胞因子对颅骨游离骨瓣存活的影响，旨在为临床实践提供理论依据和指导。

2. 机械环境

机械环境在骨折愈合过程中起着重要作用。Lu Chuanyong 等[3]在成年小鼠中建立了稳定和非稳定的胫骨骨折模型，在伤后 3 天观察到非稳定型骨折比稳定型骨折有更多的血管生成。Jagodzinski 等[4]的研究显示骨瓣早期的微运动促进了矿物质密度和硬度的增加，在骨愈合后期对骨瓣进行牵张则降低了骨密度。Lienau 等人[5]发现在截骨后 6 周，稳定性较差的骨折中血管生成较少。由此可以推测，在骨折早期不稳定固定可以促进血管生成，有利于骨愈合，而在骨折晚期，机械不稳定性则不利于血管生成。同时，多项研究表明，随着骨折间隙大小的增加，愈合率显著降低[4] [6]-[8]，0.2~1 mm 的骨折间隙可刺激愈伤组织的产生，大于 2 mm 的骨折间隙可能导致骨折延迟愈合。

3. 骨膜和硬脑膜

Özerdem 等人[9]在研究骨膜和硬脑膜在坏死颅骨愈合中的作用时，将小鼠颅骨骨瓣进行高压灭菌，使骨片完全失活，根据是否保留骨膜和硬脑膜，将小鼠分为 4 组。组织学检查显示无骨膜和硬脑膜覆盖的骨瓣大部分坏死，有硬脑膜或骨膜覆盖的骨瓣均可见成骨活性，但存在一定的失活区域，而同时覆盖骨膜和硬脑膜的骨瓣成骨活性最强。DXA 结果显示在保留硬脑膜覆盖的情况下，不论有无骨膜覆盖，骨瓣的骨密度没有显著性差异。但缺少骨膜或(和)硬脑膜覆盖的骨瓣的活骨细胞明显少于其他组。Gosain 等[10]的研究将兔子模型分为冰冻骨瓣和新鲜骨瓣组，再根据有无骨膜或(和)硬脑膜屏障将上述两组分别分为 4 个亚组，结果显示两组骨瓣均有新骨形成，且新鲜骨瓣的成骨量更加显著。没有颅骨膜屏障的新鲜骨瓣与有屏障的新鲜骨瓣相比，新骨形成略有增加，但这种差异没有统计学意义，但在颅骨膜屏障存在的情况下，新骨的颅骨膜的成分在统计学上显著降低。与有硬脑膜屏障的新鲜骨瓣相比，无硬脑膜屏障的新鲜骨瓣的新骨形成总量显著增多。这两项研究均表明，骨膜和硬脑膜可促进缺乏或无成骨活性的游离颅骨骨瓣的新骨形成，其中，硬脑膜的作用更加显著。Yuankun Zhai 等[11]评估了受伤前后骨膜和硬脑膜的骨骼和血管形成，研究中部分小鼠了接受人甲状旁腺激素(rhPTH)治疗，结果表明，无论是否接受 rhPTH 治疗，受伤后沿硬脑膜表面的新骨形成都是沿骨膜表面的新骨形成的三倍。这进一步验证了硬脑膜在成骨中的重要作用。

有研究指出骨膜、硬脑膜、骨瓣本身等的存在可以作为屏障，防止周围软组织的纤维细胞侵入骨缺损区域，允许间充质细胞迁移和血管从邻近软组织增殖到骨缺损中来促进骨再生[9] [12]。此外，骨膜和硬脑膜可以分泌多种生长因子促进骨组织的再生[13]-[17]。与成熟硬脑膜相比，未成熟动物的硬脑膜具有更强的成骨能力[18] [19]。Greenwald 等[20]的研究表明，未成熟硬脑膜中转化生长因子-β3 (TGF-β3)、胶

原蛋白-III、碱性磷酸酶 mRNA 的表达高于成熟硬脑膜，且存在数量更多的成骨样细胞。

4. 细胞因子

细胞因子在颅骨愈合过程中发挥着关键作用，它们通过调节骨细胞的增殖、分化和迁移，促进骨组织的修复和再生。研究表明，颅骨中表达的细胞因子种类丰富，包括胰岛素样生长因子(IGFs)、转化生长因子(TGF-β)、血小板源性生长因子(PDGF)、基质金属蛋白酶(MMPs)及其抑制因子(TIMPs)等。

骨形态发生蛋白(BMP)：BMP 是 TGF-β 家族中最大的亚群，BMP 信号通路在骨骼发育、组织修复和多种疾病中起关键作用[21]。同种异体移植物缺乏含有成骨活性的细胞，添加 BMPs 已被证明可以通过在移植物和宿主骨之间的界面启动新骨形成来促进愈合[22] [23]。此外，BMPs 还可以增强颅缝来源干细胞的成骨能力。Yuxing Guo 等[24]在小鼠颅骨上建立了横跨矢状缝的矩形骨缺损，通过观察发现 Gli1 + 间充质干细胞(Mesenchymal Stem Cells, MSCs)可以产生骨祖细胞，这些骨祖细胞在颅缝中显示出活跃的 BMP 信号活性。另一项研究显示，编码 BMP2 的颅缝来源干细胞能够促进颅骨临界骨缺损的愈合[25]。目前，由生物材料为基础的支架结合 BMP-2 的骨组织工程已被用于治疗严重骨缺损[26] [27]，此外，BMP 也被用于植骨手术中。

调节性 T 细胞(Tregs)：Tregs 存在于身体的多个组织器官中，通过对抗过度的免疫反应并恢复免疫稳态，促进伤口愈合和组织修复[28]。骨损伤后，局部产生炎症反应，随后产生必要的抗炎信号，使干细胞启动骨修复[29] [30]。Einhorn [31]提到骨折局部 Tregs 数量增加，这些细胞在软骨内骨形成的早期阶段赋予了局部的免疫耐受性，并在干细胞募集和软骨形成过程中通过抑制 T 细胞的增殖为发育中的组织提供了保护。Al-Sebaei 等人[32]的研究中观察到 Tregs 在骨折愈合时的软骨吸收阶段也具有抑制自身免疫的功能。另一项研究显示对照组骨髓干细胞在损伤后立即聚集在骨痂中，随后被激活，并产生丰富的骨祖细胞和成熟的成骨细胞用于骨修复，而 Treg 敲除组骨痂中的总骨干细胞谱系细胞、基质祖细胞和成熟骨谱系细胞等的百分比显著降低，表明 Tregs 除了可以通过调节免疫来促进骨修复外，还可以与骨髓干细胞直接相互作用[33]。

5. 其他

两项对经鼻内镜术后使用原位骨瓣进行颅底重建，影响原位骨瓣愈合的相关因素的研究显示，高尿素水平可以促进骨瓣愈合，而较高的术前白细胞计数、血小板计数与淋巴细胞计数比值、BMI 则不利于骨愈合[34] [35]。

6. 总结

颅骨游离骨瓣的存活和愈合是一个复杂的生物学过程，受到多种因素的综合影响。机械稳定性为骨瓣的愈合提供了必要的物理条件，骨膜和硬脑膜作为颅骨的重要附属结构，通过提供丰富的细胞成分和生长因子，显著促进了骨瓣的成骨和血管化。尽管目前的研究已经揭示了这些因素在颅骨愈合中的重要作用，但仍有许多问题有待进一步探讨。例如，颅骨与其他骨骼在细胞因子表达上的差异机制尚未完全明确，且硬脑膜和骨膜在不同病理状态下的具体作用仍需深入研究。未来的研究应聚焦于这些关键问题，通过多学科交叉合作，进一步优化颅骨游离骨瓣移植的临床策略，提高骨瓣存活率和患者预后。

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