富血小板血浆软骨下骨注射治疗膝骨关节炎的研究进展

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摘　要　膝骨关节炎(knee osteoarthritis,KOA)是骨科临床常见的一种慢性退行性疾病,目前尚无明确能够阻止或逆转 KOA 进展的治疗方法。富血小板血浆(platelet rich plasma,PRP)是富含血小板的血浆制品,在修复软骨损伤方面具有显著优势。随着对软骨下骨研究的不断深入,许多学者开展了关于 PRP 软骨下骨注射治疗 KOA 的研究。本文对软骨下骨和 PRP 进行了概述,并从作用机制和临床疗效 2 个方面就 PRP 软骨下骨注射治疗 KOA 的研究进展进行了综述。

关键词　骨关节炎,膝;富含血小板血浆;软骨下骨;注射;综述

膝骨关节炎(knee osteoarthritis,KOA)是一种慢性退行性疾病,主要临床表现为膝关节疼痛和功能障碍。目前尚无明确能够阻止或逆转 KOA 进展的治疗方法,临床上常采用口服非甾体抗炎药、关节腔内注射皮质类固醇或透明质酸等非手术疗法缓解症状[1-2];对于晚期 KOA 患者,常采用全膝关节置换术进行治疗[3]。KOA 的病理特征包括关节软骨变性、软骨下骨硬化或囊变、关节边缘骨质增生、滑膜炎性病变、关节囊挛缩、韧带松弛或挛缩、肌肉萎缩无力等[4]。软骨下骨和滑膜病变会加速关节软骨退变,而关节软骨退变会进一步影响软骨下骨和滑膜,最终导致关节功能丧失。因此,软骨下骨病变是 KOA 发生与发展的关键因素之一[5-6]。富血小板血浆(platelet rich plasma,PRP)富含多种活性生长因子,能够刺激软骨细胞增殖分化,促进胶原蛋白合成,抑制软骨炎症反应,调节受损组织环境,延缓 KOA 进展。PRP 关节腔内注射在临床上广泛应用并取得了良好的临床疗效[7-10]。随着对软骨下骨研究的不断深入,采用 PRP 软骨下骨注射治疗 KOA 的研究逐渐增多[11-13]。本文对软骨下骨和 PRP 进行了概述,并从作用机制和临床疗效 2 个方面就 PRP 软骨下骨注射治疗 KOA 的研究进展进行了综述。

1　软骨下骨概述

1.1　软骨下骨的结构和功能　软骨下骨与关节软骨形成骨软骨复合体,对于维持关节的稳定性和功能具有重要作用[14]。软骨下骨位于软骨钙化层下,由邻近钙化软骨的致密皮质骨(软骨下骨板)和靠近髓腔的松质骨(骨小梁)组成[15]。软骨下骨板厚度为 1 ~ 3 mm,具有明显的孔隙结构,其主要作用是为关节软骨提供支撑[16]。骨小梁为多孔结构,内含血管、神经和骨髓,能够调节关节软骨的营养供给和新陈代谢,且具有减震和支撑作用[17]。软骨下骨在关节中担负着重要的生理功能:软骨下骨及其周围的肌肉、肌腱等组织能够承担膝关节 30% ~50% 的负载,对减轻关节软骨负载具有重要作用[18];软骨下骨和关节软骨间不断进行物质交换和信息交流,维持关节软骨的生理活动[19]。

1.2　软骨下骨在 KOA 中的病变特征　KOA 患者的膝关节软骨、软骨下骨及关节周围的滑膜、韧带、肌肉等组织均存在不同程度的结构改变。随着对骨关节炎发病机理研究的不断深入,软骨下骨病变在骨关节炎发生和发展过程中的重要作用逐渐引起研究者的重视[20]。但目前关于软骨下骨病变是关节软骨退变的诱因还是关节软骨退变的继发损伤尚存在争议[21]。Anderson - Mackenzie 等[22]建立了豚鼠自发性 KOA 模型研究软骨下骨与关节软骨的病变发生顺序,结果显示软骨下骨病变先于关节软骨病变发生。

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然而,Stupina 等[23]的研究表明关节软骨病变先于软骨下骨硬化。

软骨下骨病变包括微损伤、骨髓水肿及囊肿等。软骨下骨微损伤包括线性微损伤和弥漫性微损伤 2 种形式:线性微损伤是指软骨下骨中存在的短裂纹,其能够导致骨转换率升高,进而导致软骨下骨板增厚、软骨钙化及潮线向透明软骨进展,但同时其也能够触发骨修复[24];弥漫性微损伤是指软骨下骨中存在大量纳米级裂缝,其能够导致软骨下骨的机械性能下降,但不会触发骨修复[25]。软骨下骨骨髓水肿常发生于软骨下骨皮质骨和松质骨间的过渡区域,多伴有骨体积增大、骨小梁增粗,与关节疼痛及 KOA 的发展关系密切[26-28]。软骨下骨囊肿是指软骨下骨中的空洞性病变,多由异常机械应力、微裂纹、水肿和局灶性骨吸收等诱导形成[27]。软骨下骨囊肿会导致患者关节疼痛加剧、骨关节炎进展迅速、关节置换风险增加[29]。软骨下骨与关节软骨关系密切,软骨下骨微损伤、骨髓水肿及囊肿等均能够导致骨软骨复合体负荷分布异常,进而引起关节软骨病变[30]。此外,KOA 不同时期软骨下骨的病变表现亦不同。KOA 早期,软骨下骨骨体积减小、微结构改变,出现局部微循环障碍,易发生应力性骨折及非典型骨髓水肿[31];KOA 中晚期,软骨下骨骨密度增加、骨量增加,软骨下骨板硬化、骨髓间隙缩小,局部微循环障碍加剧,骨髓水肿范围扩大,软骨下骨囊肿形成[32]。

2 PRP 概述

PRP 是指将自体外周血通过离心等方法获得的富含血小板的血浆制品,其血小板浓度是正常血液的 3 倍以上;PRP 注射具有无免疫排异反应、安全性高的特点[33]。PRP 中含有的血小板衍生生长因子、血管内皮生长因子等多种生长因子能够促进Ⅱ型胶原和蛋白多糖生成,进而促进软骨细胞修复和增殖、抑制软骨细胞凋亡;纤维蛋白能够促进软骨前体细胞粘附、迁移,进而促进软骨血管区重建及软骨纤维支架合成,修复软骨损伤[34-35]。随着研究的不断深入,PRP 的种类不断增加,目前常见的有富血小板纤维蛋白、富白细胞、贫白细胞等多种 PRP[36]。然而,由于 PRP 的制备方法、组分标准、分类标准以及使用方法均存在差异,导致 PRP 治疗 KOA 的临床研究结果存在一定的差异,临床数据不能整合处理[37]。因此,应从标准化方面进一步开展 PRP 治疗 KOA 的临床研究[38]。

3 PRP 软骨下骨注射治疗 KOA 的临床研究

关节腔内药物注射是治疗 KOA 的主要方法之一,目前常用的药物有皮质类固醇、透明质酸和 PRP 等。关节腔内长期注射皮质类固醇会导致软骨代谢失衡及骨质疏松[39];关节腔内注射透明质酸能够润滑关节,缓解疼痛等症状,但不能修复软骨损伤和延缓 KOA 进展[40-41]。关节腔内注射 PRP 既能减轻症状,又能够促进关节软骨修复,在一定程度上能够遏制 KOA 进展,但该方法仅能作用于关节软骨和滑膜,而不能作用于软骨下骨[35]。软骨下骨病变是 KOA 的主要病变特征之一,在 KOA 的发生和发展过程中起着重要作用。相关研究表明 PRP 软骨下骨注射治疗 KOA 在缓解膝关节疼痛、改善膝关节功能方面更具优势[42]。

3.1 PRP 软骨下骨注射治疗 KOA 的作用机制

PRP 富含多种生长因子,且能够较好地在软骨损伤区域聚集[43]。采用 PRP 软骨下骨注射治疗 KOA,PRP 浸润骨软骨复合体及间充质干细胞(mesenchymal stem cell,MSC),通过抑制炎症反应、促进组织修复、抑制氧化应激及调控 MSC 增殖分化等作用机制延缓 KOA 进展[44]。

3.1.1 抑制炎症反应及促进组织修复 炎症反应是 KOA 发生的关键因素。Xu 等[45]研究表明,PRP 中的肝细胞生长因子、胰岛素样生长因子-1 能够抑制滑膜成纤维细胞、软骨细胞和成骨细胞中的 NF-κB 信号通路,减少肿瘤坏死因子-α、白细胞介素-1β 的合成,进而阻断炎症反应过程。Anitua 等[46]研究表明,PRP 中的胰岛素样生长因子-1、血小板衍生生长因子和转化生长因子-β1 能够调控软骨和软骨下骨细胞的代谢,维持蛋白多糖的合成和降解平衡,并能够刺激软骨细胞的增殖。Vasina 等[47]研究表明,PRP 中的多种生长因子及血小板微粒能够增加 M2 巨噬细胞的表达,进而促进局部组织修复。PRP 能够通过多种生物途径发挥抗炎和促进组织修复的作用,进而延缓和治疗 KOA。

3.1.2 抑制氧化应激 PRP 能够激活成骨细胞中的抗氧化反应元件,抑制活性氧,保护细胞免受氧化应激的影响[48]。Liu-Bryan 等[49]研究表明,PRP 通过抑制氧化应激,减缓软骨下骨的分解。PRP 抑制氧化应激能够恢复软骨下骨所在的生物学环境,对软骨下

骨的骨重塑和神经血管生长有促进作用。

3.1.3　调控 MSC 增殖分化　MSC 具有分化为骨细胞、软骨细胞的能力,对于 KOA 的治疗具有重要作用[50]。KOA 患者关节中的 MSC 活性降低,向骨细胞、软骨细胞分化的能力受到抑制[51]。Everts 等[36]研究表明,骨关节炎患者关节滑液中 MSC 含量增加,且大多数 MSC 是病态的或衰老的,且滑液中高水平的 MSC 与骨关节炎的严重程度密切相关。Muinos - Lopez 等[52]的研究结果表明,软骨下骨和关节腔内联合应用 PRP 可减少 KOA 患者膝关节滑液中 MSC 的含量,然而单纯关节腔内应用 PRP 不会引起滑液中 MSC 含量的变化,提示 PRP 软骨下骨注射在调节关节内环境中具有潜在作用。PRP 浸润 MSC 能够增强 MSC 的细胞活性及分化能力,促进其向骨细胞、软骨细胞分化,进而修复骨软骨损伤。

3.2　PRP 软骨下骨注射治疗 KOA 的临床疗效　目前,PRP 软骨下骨注射治疗 KOA 的临床研究仍处于起步阶段。Sanchez 等[53]采用 PRP 软骨下骨注射治疗 KOA,取得良好的治疗效果。Lychagin 等[54]采用 PRP 软骨下骨注射治疗 17 例骨关节炎合并骨髓水肿患者,治疗 1 年后,患者西安大略和麦克马斯特大学骨关节炎指数(Western Ontario and McMaster Universities osteoarthritis index,WOMAC)评分和膝关节损伤和骨关节炎结局评分(knee injury and osteoarthritis outcome score,KOOS)均明显降低,且治疗后 1 ~ 3 个月内软骨低聚基质蛋白血清含量持续升高,且在治疗后 6 个月、12 个月软骨低聚基质蛋白血清含量与治疗后 3 个月相当;提示 PRP 软骨下骨注射治疗效果持续时间较长,能够显著改善患者生活质量。Sanchez 等[55]采用关节腔内和软骨下骨联合注射 PRP 的方法治疗严重 KOA 患者 14 例,分别于关节腔内和软骨下骨注射 8 mL 和 5 mL 的 PRP,每隔 7 d 注射 1 次,连续注射 3 次,治疗后6 个月,患者的 KOOS 和关节滑液中 MSC 含量均显著降低。Sanchez 等[56]还比较分析了关节腔内和软骨下骨联合注射 PRP 和单纯关节腔内注射 PRP 治疗严重 KOA 的临床疗效,结果显示治疗后 2 个月、6 个月、12 个月,联合注射治疗组患者 WOMAC 评分和 KOOS 显著高于单纯注射治疗组,治疗后 6 个月、12 个月联合注射治疗组达到最小临床有意义改善的患者数量显著多于单纯注射治疗组。苏柯等[57]分别采用关节腔内和松质骨内联合注射 PRP(联合治疗组)和单纯关节腔内注射 PRP(单纯治疗组)治疗 KOA,结果显示2 组患者膝关节疼痛缓解、功能改善,治疗后 12 个月联合治疗组患者膝关节疼痛视觉模拟量表评分和 WOMAC 评分均低于单纯治疗组。Su 等[58]对比了关节腔内和骨内联合注射 PRP、单纯关节腔内注射 PRP 和关节腔内注射透明质酸治疗 KOA 的临床疗效,18 个月随访结果显示关节腔内和骨内联合注射 PRP 能够持续改善膝关节功能、缓解膝关节疼痛,提高患者生活质量。PRP 软骨下骨注射治疗 KOA 具有良好的临床疗效,而 PRP 关节腔内和软骨下骨联合注射治疗 KOA 表现出更佳的效果。

4　小　结

KOA 作为骨科临床常见病,目前尚无明确能够阻止或逆转其进展的治疗方法。PRP 内含有丰富的生长因子,在修复软骨损伤方面具有显著优势,且 PRP 关节腔内注射治疗 KOA 具有良好的临床疗效。软骨下骨与关节软骨形成骨软骨复合体,其病变在 KOA 的发生发展过程中起着重要作用。PRP 软骨下骨注射能够通过抑制炎症反应、促进组织修复、抑制氧化应激及调控 MSC 增殖分化等作用机制延缓 KOA 进展。PRP 关节腔内和软骨下骨联合注射治疗 KOA 的临床疗效显著优于单纯 PRP 关节腔内注射,且疗效持续时间更长。目前,PRP 软骨下骨注射治疗 KOA 的临床研究尚处于起步阶段,但其可能成为未来 KOA 治疗的重要方向。

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