Advances in Clinical Medicine 临床医学进展, 2024, 14(1), 285-291
Published Online January 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.141041

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富血小板血浆在子宫内膜损伤修复中的研究进展

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收稿日期：2023年12月8日；录用日期：2024年1月2日；发布日期：2024年1月9日

摘　要

子宫内膜损伤是生殖医学中面临的棘手问题，常由严重创伤或感染所致。临床上常表现为不孕，反复流产以及反复种植失败。改善生育结局仍是子宫内膜损伤治疗中的难点。富血小板血浆是抽取外周血液，通过离心方式获取的血小板浓缩物，富含多种生长因子，近年来被广泛应用于组织的再生修复。本文旨在通过综述富血小板血浆在子宫内膜损伤修复中的作用机制以及研究现状，为修复子宫内膜损伤提供新思路。

关键词

富血小板血浆，薄型子宫内膜，宫腔粘连，反复种植失败，子宫内膜炎，子宫内膜损伤修复

Progress of Platelet-Rich Plasma in the Repair of Endometrial Injury

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Received: Dec. 8th, 2023; accepted: Jan. 2nd, 2024; published: Jan. 9th, 2024

Abstract

Endometrial injury is a difficult problem faced in reproductive medicine, often caused by severe trauma or infection. It often presents clinically as infertility, recurrent miscarriages and repeated implantation failures. Improving fertility outcomes remains a difficult part of treatment. Platelet-rich plasma is a platelet concentrate obtained by centrifugation of peripheral blood, which is rich in various growth factors and has been widely used for regenerative repair of tissues in re-

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文章引用: 汤若楠, 孙港港. 富血小板血浆在子宫内膜损伤修复中的研究进展[J]. 临床医学进展, 2024, 14(1): 285-291. DOI: 10.12677/acm.2024.141041

cent years. The aim of this paper is to review the mechanism of platelet-rich plasma in the repair of endometrial injury and the current status of research to provide new ideas for the repair of endometrial injury.

Keywords

Platelet-Rich Plasma, Thin Endometrium, Uterine Adhesions, Repeated Implantation Failures, Endometritis, Endometrial Damage Repair

1. 概述

子宫内膜是孕育生命的土壤，是女性生殖健康的关键组成部分。当子宫内膜受到严重损伤，比如反复刮宫、感染等病理情况下，子宫基底层受到损伤，基底层细胞增殖能力受损，其最直接的表现是子宫内膜变薄[1]。同时，受损严重的子宫内膜在修复的过程中可能发生病理性修复，产生程度不等的纤维化，严重时甚至导致宫腔粘连引起宫腔闭塞[2]。子宫内膜受损易导致月经减少[3]、闭经[2]、反复流产及不孕[4]，在体外受精胚胎移植过程中的可能表现为反复种植失败(Recurrent implantation failure, RIF)。因此，子宫内膜的损伤修复是生殖领域需要解决的难点问题。

富血小板血浆(platelet rich plasma, PRP)是抽取外周血液，通过离心方式获取的血小板浓缩物，主要成份是血小板、纤维蛋白和白细胞[5]。同时血小板激活后释放多种生长因子，可发挥组织再生的作用。临床上用作治疗的 PRP 来源于自身外周血液，没有病毒感染及自身免疫的风险，且无伦理学争议。另外，PRP 具备制备简单、快速及经济等优点。因此，PRP 在骨科[6]、皮肤科[7]、口腔科[8]以及妇科[9]等多个医学学科中有着广泛的应用。现综述富血小板血浆在子宫内膜损伤修复中的作用机制及研究进展，为子宫内膜损伤修复提供新的研究方向。

2. PRP 修复受损子宫内膜的机制研究

血小板分泌的生长因子包括血小板衍生生长因子(platelet-derived growth factor, PDGF)、表皮生长因子(epidermal growth factor, EGF)、胰岛素样生长因子 1 (insulin-like growth factor, IGF1)、转化生长因子-β (transforming growth factor, TGF-β)以及血管内皮细胞生长因子(vascular endothelial growth factor, VEGF [10]。这些生长因子是 PRP 的主要成分，在组织再生、血管重塑、血管生成、炎症反应等过程中起着非常重要的作用。

PDGF 能够促进血管生成，上皮细胞的形成以及成纤维细胞的增殖。释放后，对单核细胞、中性粒细胞和成纤维细胞具有趋化作用[11]。PDGF 还影响细胞生长、细胞迁移、代谢效应，并调节细胞膜受体，在伤口愈合、动脉粥样硬化、纤维化中发挥重要作用[12]。EGF 由巨噬细胞、成纤维细胞和 PLT 分泌，对成纤维细胞、角质形成细胞和内皮细胞有丝分裂作用，增加胶原酶的活性和上皮细胞的血管生成，加速慢性伤口的愈合和表皮的再生。TGF-β 属有三种亚型(TGF-β1、β2 和 β3)，主要在血小板和巨噬细胞中产生。TGF-β 引起单核细胞、巨噬细胞和成纤维细胞的趋化和激活，增加纤维连接蛋白、整合素和胶原蛋白的合成，刺激血管生成，支持长期伤口愈合和骨再生[13]。IGF-1 在许多组织中具有自分泌和旁分泌作用。IGF-1 促进成骨细胞增殖并刺激骨钙素合成。在软骨形成、脂肪形成、肌肉形成等过程中刺激间充

质干细胞增殖分化，促进神经元分化，诱导血管内皮细胞趋化，是细胞凋亡的重要调节因子[14]。

2.1. 促子宫内膜细胞增殖和血管生成作用

PRP 能够促进子宫内膜细胞增殖，并且通过诱导血管内皮细胞的迁移、增殖及分化，从而促进新生血管生成。基质金属蛋白酶(MMPs)通过细胞外基质(ECM)降解和伤口重塑参与组织再生和伤口愈合[15]。PRP 中存在多种已知可激活 MMP 生长因子[16]。一项动物实验[17]将 PRP 与子宫内膜基质细胞共培养，发现 PPP 在一定程度上调了基质降解酶 MMP1，MMP3，MMP7 和 MMP26 的表达。另一项动物研究显示，PRP 诱导 BMSCs IGF-1 表达，并通过激活 NF-KB 途径，上调 IL-10 的表达，从而增强 BMSCs 的分化潜能。PRP 联合 BMSCs 移植能够显著增加大鼠子宫内膜的厚度，加速受损子宫内膜的修复和再生[18]。

2.2. 抑制纤维化作用

Kim [19]通过建立子宫内膜损伤小鼠模型，PRP 治疗后 7 天被安乐死，用组织学和免疫荧光染色，以及纤维化标志物表达水平的测量的方法评估小鼠子宫内膜纤维化和再生的细胞和分子特征。研究发现未接受 PRP 治疗组的组织切片表现为子宫内膜腔狭窄，萎缩柱状上皮，管腔丢失，基质很少。在 PRP 处理组中观察到增殖的腺体和子宫内膜基质细胞。未处理组 Masson 三色染色显示有子宫内膜纤维化的迹象，而 PRP 处理的子宫内膜胶原蛋白沉积显着降低。纤维化相关因子(Collal，Tgfβ1 和 Timp1)表达降低。研究表明，PRP 促进了子宫内膜结构的恢复，抑制了子宫角损伤后的纤维化。

2.3. 抗炎作用

PRP 中血小板激活后分泌的炎性趋化因子和所含的高浓度白细胞，在抑制机体的炎症反应和控制感染方面具有重要作用[20] [21]。Jang [22]的一项动物实验表明与对照组相比，PRP 处理组的促炎症细胞因子 IL-1β mRNA 的表达水平明显降低，而 c-Kit mRNA 上调。这表明 PRP 可以上调抗炎因子的表达水平，抑制子宫内膜中炎症因子的释放和过度的炎症反应。

3. PRP 在子宫内膜损伤中的临床应用

3.1. 薄型子宫内膜

薄型子宫内膜通常定义[23]为在辅助生殖技术周期中，给予人绒毛膜促性腺激素当天，超声下显示子宫内膜厚度 < 7 mm。研究发现，子宫内膜过薄可导致反复种植失败、体外受精－胚胎移植治疗周期取消，甚至可能增加妊娠成功后子痫前期、胎盘早剥等产科妊娠并发症的风险，导致临床妊娠率、活产率显著降低[24]。2015 年中山大学梁晓燕团队[25]首次将 PRP 输注到 5 名薄型子宫内膜患者的宫腔，治疗后所有患者的子宫内膜均有增长和获得临床妊娠。2023 年[26]的一项前瞻性随机对照研究，将 120 名薄型子宫内膜患者随机分组，研究结果显示接受 PRP 灌注组的子宫内膜厚度和临床妊娠率显著增加。

3.2. 宫腔粘连

IUA 是由于各种原因造成子宫内膜基底层受损后发生纤维化，导致宫腔内壁之间纤维组织粘连形成，宫腔容积变小，宫腔变形，甚至出现宫腔封闭[4]。通常伴有月经减少或者闭经、周期性盆腔痛、不孕及复发性流产等[27]。2018 年的一项[28]病例报告首次报道了 PRP 在 2 例宫腔粘连管理中的应用，该研究表明 PRP 不仅可以促进子宫内膜生长，还可能改善子宫内膜功能。自此出现了多项高质量的探索 PRP 治疗宫腔粘连的临床研究。Wang [29]等报道，与对照组相比，富血小板纤维蛋白组粘连严重程度评分明显下降，临床妊娠率和月经时间明显改善，并且未发现任何不良事件。沈[30]招募了中度至重度 IUA 女性，并将其随机分配到 PRP 或对照组。PRP 组在宫腔镜粘连松解术后使用适合宫内的球囊联合 PRP 输注进行

治疗，而对照组仅接受球囊治疗。结果发现宫内 PRP 输注有利于减少 TCRA 术后粘连重塑。另外，两项高质量的 Meta 分析[31] [32]结果表明 PRP 可以改善宫腔粘连患者的临床预后。因此，PRP 在宫腔粘连治疗中的潜力已经得到证实，对临床应用具有重要意义。

3.3. 反复种植失败

反复种植失败(RIF)是辅助生殖技术中一大难题，影响了高达 10%的体外受精(IVF)患者[33]。目前对于 RIF 的定义仍然存在争议。较多接受的定义是，在至少三个新鲜/冷冻周期内移植至少四个优质胚胎后，未能实现临床妊娠[34]。子宫内膜容受性差是 RIF 的其中一个因素。Xu [35]的一项研究对 288 例 RIF 患者的病历资料进行回顾性分析，根据患者在 FET 周期胚胎移植前是否接受 PRP 宫内灌注分为两组。结果显示 FET 周期胚胎移植前宫内灌注 PRP 可显著提高 RIF 患者的活产率和临床妊娠率。一项 meta 分析[36]研究评估了宫内灌注 PRP 对复发性着床失败 RIF 女性妊娠结局影响，共纳入 6 项随机对照研究贺 4 项队列研究，分析结果表明，与对照组相比，接受 PRP 治疗的妇女的妊娠结局，包括临床妊娠率、化学妊娠率、着床率、活产率和流产率都有所改善。

3.4. 子宫内膜炎

慢性子宫内膜炎(chronic endometritis, CE)通常在组织学上诊断为浆细胞浸润子宫内膜间质[37]。是由多种细菌病原体引起的子宫内膜持续炎症状态[38]。在 CE 子宫内膜中，包括趋化因子、细胞因子和凋亡蛋白在内的多种基因的局部表达失调[39]。CE 患者虽无明显临床症状，但严重影响女性生殖健康。有研究报道，不孕患者的 CE 发生率为 2.8%至 56.8%，CE 的存在与 ART 的总体成功率较低有关[40]。2023 年武汉大学人民医院生殖医学中心[41]报道了 PRP 在 RIF 合并慢性子宫内膜炎(CE)中的应用。将 RIF 患者分为 CE(+)组和 CE(−)组，给予 CE(+)组盐酸多西环素和甲硝唑治疗 14 天后复查；若为 CE 强阳性，给予 PRP 及抗生素治疗，并再次复查。研究发现 CE(−)组 hCG 阳性率、临床妊娠率和着床率显著升高，研究结果表明 PRP 治疗可显著改善 FET 周期 CE 阴性转化患者的妊娠结局。

4. PRP 的给药方式

根据制备方法的不同，可以分为一代血小板浓缩物 PRP 和富含血小板的纤维蛋白(PRF)。与 PRP 呈流动性液体不同的是，PRF 是二代血小板浓缩物，呈现为流动性差的凝胶结构[42]。二者的成分相差不大，主要含有纤维蛋白、血小板和白细胞。区别在于 PRF 在制备过程中不使用抗凝剂。目前这些临床研究中所用到的大多数为一代 PRP，在给药剂量、给药时间、给药次数、给药方式方面有所差异。大多数研究采用 PRP 宫腔内的直接灌注。这种灌注方式使 PRP 浮于子宫内膜表面，易使 PRP 受到子宫收缩力和重力的影响，PRP 灌注不久后流出宫腔。存在药物作用时间短、剂量少等缺点。另外有研究在手术后即刻灌注 PRP，这样术后子宫内残存液体会对 PRP 进行稀释，降低 PRP 的药效。有学者[43]提出在宫腔镜下将 PRP 注射到子宫内膜下层这种给药方式，达到使足量 PRP 长时间留存于宫腔的效果，持续发挥促内膜生长的作用。2021 年[44]发表的一篇研究比较了子宫内膜注下射 PRP (subendometrium, SE-PRP)宫内灌注 PRP (intrauterine, IU-PRP)对于 RIF 患者的妊娠结局。IU-PRP 是经腹部超声引导下通过 ET 导管将大约 1 mL 的 PRP 注入子宫腔。SE-PRP 是使用 ET 导管的取卵针(18G, 330 mm)经阴道将 PRP 注射到内膜下。结果显示，对于 RIF 患者，IU-PRP 与 SE-PRP 在改善妊娠结局上没有统计学差异。

5. 小结

PRP 富含多种生长因子和细胞因子，在子宫内膜损伤修复中发挥促子宫内膜细胞增殖、促血管生成、抑制纤维化以及抗炎作用。从目前现有研究来看，PRP 在子宫内膜损伤修复中的应用尚未发现不良事件。

PRP 能够一定程度上促进子宫内膜修复，改善妊娠结局。然而，在 PRP 的临床应用中，没有给出标准的用药方案。在制备方式、治疗剂量、治疗时间以及次数等方面存在争议。为了规范 PRP 的治疗效果及用药方案，未来仍需要大量的高质量临床研究对其进行探索。

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