

关节镜下微骨折术联合富血小板血浆与纤维蛋白凝胶覆盖微骨折创面治疗膝骨关节炎软骨退变缺损

高文香, 王明君, 李晓峰, 李鹏, 杨鑫, 王鸿雁, 邹春雨, 郝军, 王冬

(河南省洛阳正骨医院/河南省骨科医院, 河南 郑州 450016)

摘要 目的: 观察关节镜下微骨折术联合富血小板血浆(platelet rich plasma, PRP)与纤维蛋白凝胶覆盖微骨折创面治疗膝骨关节炎(knee osteoarthritis, KOA)软骨退变缺损的临床疗效和安全性。方法: 将符合要求的 KOA 软骨退变缺损患者随机纳入联合组或微骨折组。联合组先于关节镜下在软骨缺损处软骨下骨行微骨折术, 然后用 PRP 与凝血酶填充微骨折处理后的软骨缺损处, 最后用纤维蛋白凝胶进行封口处理。微骨折组仅进行微骨折处理。术前及术后随访时, 测定患者上下 10 级楼梯后的膝关节疼痛视觉模拟量表(visual analogue scale, VAS)评分, 测量同一位置软骨退变缺损面积, 测定患者的西安大略和麦克马斯特大学(Western Ontario and McMaster Universities, WOMAC)骨关节炎指数。观察治疗及随访期间的并发症发生情况。结果: 共纳入 32 例患者, 联合组和微骨折组各 16 例。所有患者均获得随访, 随访时间 10~15 个月, 中位数 12 个月。治疗及随访期间均未出现并发症。治疗前 2 组患者的膝关节疼痛 VAS 评分比较, 差异无统计学意义[(6.67 ± 1.05)分, (6.60 ± 1.30)分, $t = 0.155$, $P = 0.878$]; 末次随访时 2 组患者的膝关节疼痛 VAS 评分均较治疗前降低($t = 10.990$, $P = 0.000$; $t = 5.641$, $P = 0.000$), 联合组的评分低于微骨折组[(2.13 ± 1.25)分, (3.38 ± 1.43)分, $t = -2.221$, $P = 0.035$]。治疗前 2 组患者的软骨退变缺损面积比较, 差异无统计学意义[(2.91 ± 0.70) cm², (2.57 ± 0.68) cm², $t = 1.354$, $P = 0.187$]; 末次随访时 2 组患者的软骨退变缺损面积均较治疗前减小($t = 6.688$, $P = 0.000$; $t = 2.772$, $P = 0.015$), 联合组的软骨退变缺损面积小于微骨折组[(1.18 ± 0.74) cm², (1.83 ± 0.76) cm², $t = -2.241$, $P = 0.022$]。治疗前 2 组患者的 WOMAC 骨关节炎指数比较, 差异无统计学意义[(108.27 ± 12.89)分, (106.87 ± 13.11)分, $t = 0.295$, $P = 0.770$]; 末次随访时 2 组患者的 WOMAC 骨关节炎指数均较治疗前减小($t = 17.318$, $P = 0.000$; $t = 17.760$, $P = 0.000$), 联合组的 WOMAC 骨关节炎指数小于微骨折组[(24.69 ± 12.53)分, (36.57 ± 14.97)分, $t = -2.354$, $P = 0.026$]。结论: 关节镜下微骨折术联合 PRP 与纤维蛋白凝胶覆盖微骨折创面, 可修复 KOA 软骨退变缺损, 减轻膝关节疼痛症状、改善膝关节功能, 安全性较高, 疗效优于单纯微骨折术治疗。

关键词 骨关节炎; 膝; 软骨; 关节成形术, 软骨下; 富血小板血浆; 纤维蛋白; 凝胶; 关节镜检查; 临床试验

Arthroscopic microfracture surgery combined with microfractured wound surface coverage with platelet rich plasma and fibrin gels for treatment of degenerative cartilage defects in patients with knee osteoarthritis

GAO Wenxiang, WANG Mingjun, LI Xiaofeng, LI Peng, YANG Xin, WANG Hongyan, ZOU Chunyu, HAO Jun, WANG Dong
Luoyang Orthopedic – Traumatological Hospital, Zhengzhou 450016, Henan, China

ABSTRACT **Objective:** To observe the clinical curative effects and safety of arthroscopic microfracture surgery combined with microfractured wound surface coverage with platelet rich plasma (PRP) and fibrin gels (FG) for treatment of degenerative cartilage defects in patients with knee osteoarthritis (KOA). **Methods:** Thirty – two patients with KOA and degenerative cartilage defects were enrolled in the study and were randomly divided into combination group and microfracture group, 16 cases in each group. The patients in combination group were treated with arthroscopic microfracture surgeries on subchondral bones, and their cartilage defects were filled with PRP and thrombin and were sealed with FG; while the patients in microfracture group were merely treated with arthroscopic microfracture surgeries. The knee pain visual analogue scale (VAS) scores were measured after the patients went up and down 10 stairs, and the area of degenerative cartilage defects and the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index were measured through the preoperative and postoperative follow – up respectively. Moreover, the complication incidences were observed and compared between the 2 groups during the treatment and follow – up period. **Results:** All patients in the 2 groups were followed up for 10 – 15 months with a median of 12 months. No complications were found in the 2 groups during the treatment and follow – up period. There was no statistical difference in knee pain VAS scores between the 2 groups before the treatment (6.67 ± 1.05 vs 6.60 ± 1.30 points, $t = 0.155$, $P = 0.878$). The knee pain VAS scores decreased at

last follow-up compared to pretreatment in the 2 groups ($t = 10.990, P = 0.000; t = 5.641, P = 0.000$), and were lower in combination group compared to microfracture group (2.13 ± 1.25 vs 3.38 ± 1.43 points, $t = -2.221, P = 0.035$). There was no statistical difference in the area of degenerative cartilage defect between the 2 groups before the treatment (2.91 ± 0.70 vs 2.57 ± 0.68 cm²), $t = 1.354, P = 0.187$). The area of degenerative cartilage defect decreased at last follow-up compared to pretreatment in the 2 groups ($t = 6.688, P = 0.000; t = 2.772, P = 0.015$), and was less in combination group compared to microfracture group (1.18 ± 0.74 vs 1.83 ± 0.76 cm²), $t = -2.241, P = 0.022$). There were no statistical difference in WOMAC osteoarthritis index between the 2 groups before the treatment (108.27 ± 12.89 vs 106.87 ± 13.11 points, $t = 0.295, P = 0.770$). The WOMAC osteoarthritis index decreased at last follow-up compared to pretreatment in the 2 groups ($t = 17.318, P = 0.000; t = 17.760, P = 0.000$), and was lower in combination group compared to microfracture group (24.69 ± 12.53 vs 36.57 ± 14.97 points, $t = -2.354, P = 0.026$). **Conclusion:** The combination therapy of arthroscopic microfracture surgery and microfractured wound surface coverage with PRP and FG can repair degenerative cartilage defect, relieve the knee pain and improve the knee function in patients with KOA, meanwhile, it has high safety and its curative effect is better than that of monotherapy of arthroscopic microfracture surgery.

Keywords osteoarthritis; knee; cartilage; arthroplasty; subchondral; platelet-rich plasma; fibrin; gels; arthroscopy; clinical trial

富血小板血浆 (platelet rich plasma, PRP) 作为多种天然生物活性因子的载体,近年来在膝骨关节炎 (knee osteoarthritis, KOA) 软骨退变缺损的治疗方面受到了越来越多的关注^[1-3]。常见的应用方法为膝关节腔注射,但 PRP 会扩散至整个关节腔,对局部软骨退变缺损的治疗作用有限^[4]。微骨折术作为刺激骨髓促进软骨生成的代表性技术,也可用于 KOA 软骨退变缺损的治疗^[5]。有研究表明,PRP 注射结合微骨折术可以增强软骨退变缺损的修复反应^[6]。对于将 PRP 局限固定于微骨折术后创面能否提高疗效,目前尚未见到相关的报道。为此,我们进行了相关的临床研究,现总结报告如下。

1 临床资料

1.1 一般资料 以 2015 年 2 月至 2018 年 2 月在河南省洛阳正骨医院 (河南省骨科医院) 住院治疗的 KOA 患者为研究对象。试验方案经过医院医学伦理委员会审查通过。

1.2 诊断标准 采用中华医学会骨科学分会制定的《骨关节炎诊治指南 (2007 年版)》中 KOA 的诊断标准^[7]。

1.3 纳入标准 ①符合上述诊断标准;②年龄 40 ~ 60 岁;③MRI 显示膝关节软骨局部全层退变缺损;④拟进行关节镜检查;⑤同意参与本研究,签署知情同意书。

1.4 排除标准 ①Kellgren-Lawrence 分级^[8]为Ⅲ级或Ⅳ级者;②膝关节症状由机械因素引起者;③患膝有手术史者;④对侧肢体存在病患者,如损伤或功能障碍等;⑤合并感染、类风湿关节炎者;⑥合并严重

内科疾病及精神疾患者。

2 方法

2.1 分组及治疗方法 所有符合要求的患者均进行关节镜检查。术前抽取 50 mL 自体静脉血,按照 Landesberg 等^[9]的方法制备 PRP。获得约 4 mL PRP,摇匀后备用。在制备 PRP 的同时,常规消毒、铺巾,上止血带。行关节镜下探查清理术,将膝关节软骨局灶性全层退变,且退变面积 ≤ 4 cm² 或退变缺损直径 < 2 cm 者,采用随机数字表随机纳入联合组或微骨折组;软骨退变未达到此标准者仅行关节镜下探查清理术,不纳入本次研究。

联合组患者行关节镜下探查清理后,继续在关节镜下在软骨退变缺损处用微骨折器进行软骨下骨微骨折钻孔,间距 3 mm,直径 2 mm,深度 2 ~ 5 mm,以松质骨内骨髓渗出为度。负压抽吸,将关节腔内的水排除干净。将 PRP 与凝血酶 (湖南一格制药有限公司) 均匀注射涂抹于钻孔处理后的软骨缺损处,再用纤维蛋白凝胶 (广州倍绣生物技术有限公司) 进行封口处理。微骨折组仅进行微骨折处理,方法与联合组相同。

术后联合组和微骨折组患者均将膝关节伸直位固定 1 周,1 周后开始不负重活动,6 周后开始部分负重,8 周后开始完全负重行走,6 个月后恢复正常活动。

2.2 疗效及安全性评价方法 术前及术后随访时测定患者上下 10 级楼梯后的膝关节疼痛视觉模拟量表 (visual analogue scale, VAS) 评分,测量同一位置软骨退变缺损面积 (将 MRI 检查所得图像以 DICOM 格式导入 MIMICS 软件中,对图像进行读取、分割,计算软

骨退变缺损面积),测定患者的西安大略和麦克马斯特大学(Western Ontario and McMaster Universities, WOMAC)骨关节炎指数^[10]。观察治疗及随访期间的并发症发生情况。

2.3 数据统计方法 采用 SPSS20.0 软件进行数据统计分析。2 组患者性别、病变侧别的组间比较均采用 χ^2 检验,年龄、病程、疼痛 VAS 评分、软骨退变缺损面积及 WOMAC 骨关节炎指数的组间及组内比较均采用 t 检验。检验水准 $\alpha=0.05$ 。

3 结 果

3.1 分组结果 共纳入 32 例患者,联合组和微骨折组各 16 例。2 组患者的基线资料比较,差异均无统计学意义,有可比性(表 1)。

3.2 疗效及安全性评价结果 所有患者均获得随访,随访时间 10~15 个月,中位数 12 个月。治疗及随访期间均未出现并发症。治疗前 2 组患者的膝关节疼痛 VAS 评分比较,差异无统计学意义;末次随访时 2 组患者的膝关节疼痛 VAS 评分均较治疗前降低,联合组的评分低于微骨折组。治疗前 2 组患者的软骨退变缺损面积比较,差异无统计学意义;末次随访时 2 组患者的软骨退变缺损面积均较治疗前减小,联合组的软骨退变缺损面积小于微骨折组。治疗前 2 组患者的 WOMAC 骨关节炎指数比较,差异无统计学意义;末次随访时 2 组患者的 WOMAC 骨关节炎指数均较治疗前减小,联合组的 WOMAC 骨关节炎指数小于微骨折组。见表 2 至表 4。典型病例图片见图 1。

表 1 2 组膝骨关节炎软骨退变缺损患者的基线资料

组别	样本量 (例)	性别(例)		年龄 ($\bar{x} \pm s$, 岁)	病变侧别(例)		病程 ($\bar{x} \pm s$, 年)
		男	女		左	右	
联合组	16	5	11	49.62 \pm 6.22	9	7	3.71 \pm 2.21
微骨折组	16	7	9	50.21 \pm 5.67	8	8	3.52 \pm 2.13
检验统计量		$\chi^2=0.533$		$t=0.798$	$\chi^2=0.125$		$t=1.031$
P 值		0.465		0.365	0.723		0.365

表 2 2 组膝骨关节炎软骨退变缺损患者的膝关节疼痛视觉模拟量表评分

组别	样本量(例)	膝关节疼痛视觉模拟量表评分($\bar{x} \pm s$, 分)		t 值	P 值
		治疗前	末次随访时		
联合组	16	6.67 \pm 1.05	2.13 \pm 1.25	10.990	0.000
微骨折组	16	6.60 \pm 1.30	3.38 \pm 1.43	5.641	0.000
t 值		0.155	-2.221		
P 值		0.878	0.035		

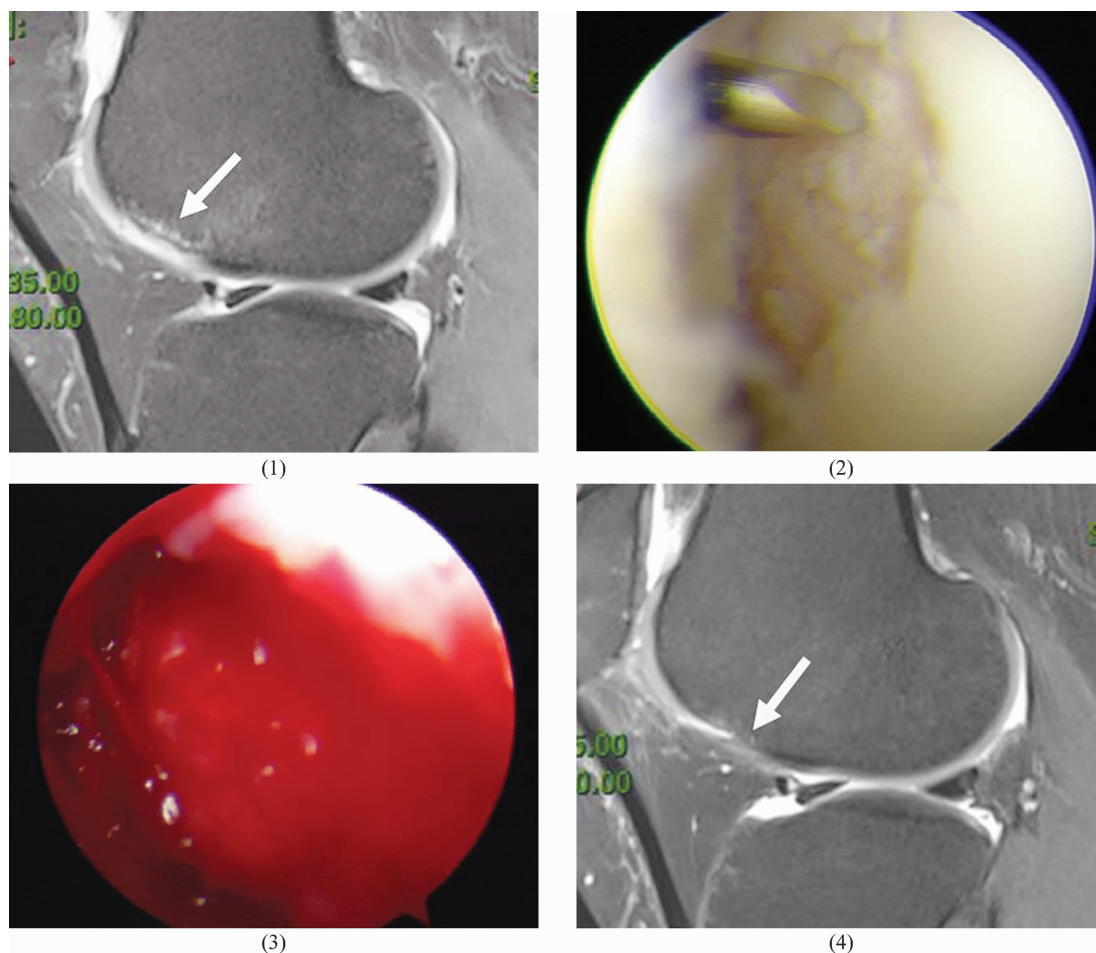
表 3 2 组膝骨关节炎软骨退变缺损患者的软骨退变缺损面积

组别	样本量(例)	软骨退变缺损面积($\bar{x} \pm s$, cm^2)		t 值	P 值
		治疗前	末次随访时		
联合组	16	2.91 \pm 0.70	1.18 \pm 0.74	6.688	0.000
微骨折组	16	2.57 \pm 0.68	1.83 \pm 0.76	2.772	0.015
t 值		1.354	-2.241		
P 值		0.187	0.022		

表 4 2 组膝骨关节炎软骨退变缺损患者的 WOMAC 骨关节炎指数

组别	样本量(例)	WOMAC 骨关节炎指数($\bar{x} \pm s$, 分)		t 值	P 值
		治疗前	末次随访时		
联合组	16	108.27 \pm 12.89	24.69 \pm 12.53	17.318	0.000
微骨折组	16	106.87 \pm 13.11	36.57 \pm 14.97	17.760	0.000
t 值		0.295	-2.354		
P 值		0.770	0.026		

WOMAC:西安大略和麦克马斯特大学



(1)术前膝关节 MRI 显示,股骨前外髌软骨全层退变缺损,面积约 3 cm^2 ; (2)关节镜下在软骨退变缺损处用微骨折器钻孔,制造软骨下骨微骨折; (3)富血小板血浆覆盖微骨折创面后用纤维蛋白凝胶封口; (4)术后 12 个月膝关节 MRI 显示,股骨前外髌软骨退变缺损大部分被修复,退变缺损面积减小至约 1 cm^2

图 1 膝关节炎软骨退变缺损治疗前后图片

4 讨论

微骨折术是在软骨下骨进行多点均匀垂直钻孔,形成粗糙表面,易于血肿黏附、填充缺损,自骨髓中渗透出的潜在干细胞可分化为纤维软骨细胞,也可修复软骨缺损^[5,11]。Namdari 等^[12]对 24 名因膝关节软骨损伤采用微骨折术治疗的美国篮球协会运动员进行了随访观察,其中 14 名重返赛场。对于股骨髌软骨缺损面积 $<4\text{ cm}^2$ 的患者,采用微骨折技术通常可取得较好的临床效果;而对于更大面积的缺损,这一技术的治疗效果往往较差^[13-14]。所以我们选择膝关节软骨退变缺损面积 $\leq 4\text{ cm}^2$ 或退变缺损直径 $<2\text{ cm}$ 的患者进行研究,治疗后退变缺损面积 $\leq 2\text{ cm}^2$ 。

PRP 被激活后,其 α 颗粒能够释放出大量细胞生长因子,如血管内皮生长因子、表皮生长因子、血小板衍生因子、碱性成纤维细胞生长因子及转化生长因子-1 等^[15]。PRP 不但能够刺激软骨细胞增殖、基质

分泌,而且能够抑制炎症因子表达和软骨细胞凋亡^[16]。高浓度的 PRP 可以在一定程度上修复 KOA 大鼠退变的关节软骨,改善运动能力^[17]。目前临床应用 PRP 治疗 KOA 主要以关节腔内注射为主^[18],但 PRP 会扩散至整个关节腔,影响治疗效果^[19]。为进一步提高软骨修复质量,出现了微骨折术联合 I/III 胶原基质介导软骨再生技术^[20]、微骨折术联合可吸收 PGA-透明质酸内植物或富血小板纤维凝胶覆盖^[21]等技术。基于以上研究,本研究用 PRP 覆盖软骨缺损处,利用其释放的多种生长因子,刺激微骨折术后骨髓中渗透出的潜在干细胞更好地向纤维软骨细胞分化,从而促进软骨修复。

用纤维蛋白凝胶将 PRP 固定于软骨缺损处也是联合组治疗效果更好的一个关键因素。纤维蛋白凝胶早已被用在骨软骨损伤修复、自体软骨移植等关节外科手术中^[22-23]。纤维蛋白原和凝血酶混合后可形

成胶冻,能附着在软骨缺损处,并形成与缺损相符的形状。用纤维凝胶封闭软骨或骨软骨缺损,纤维凝胶可牢固附着在骨缺损处^[22,24]。但也有尸体标本实验显示,以同种异体骨微小颗粒填充软骨缺损,纤维凝胶封口后立刻活动膝关节,填充物会发生移位,建议移植物填充软骨缺损后限制活动度^[25]。因此,我们在术后 1 周内限制患肢活动。Brennan 等^[26]对 KOA 患者的 MRI 进行了跟踪评估,结果表明自然状态下 KOA 软骨缺损面积会随着时间推移逐渐进展,每年的进展速度为 2.5%。本研究中的 2 组患者,其软骨退变缺损不但没有随时间推移而进展,反而均有不同程度改善,其中联合组改善更明显。提示 2 种治疗方案均有效,其中联合组的疗效更好。

本研究的结果提示,关节镜下微骨折术联合 PRP 与纤维蛋白凝胶覆盖微骨折创面,可修复 KOA 软骨退变缺损,减轻膝关节疼痛症状、改善膝关节功能,安全性较高,疗效优于单纯微骨折术治疗。但由于样本量较小、随访时间较短,所得结论还有待于进一步的研究证实。

5 参考文献

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